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Medical
Water

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Original Communications

ESTIMATION OF VALVE AREA AND "VALVULAR RESISTANCE"

A CRITICAL STUDY OF THE PHYSICAL BASIS OF THE METHODS EMPLOYED

F. A. RODRIGO, M.S.

INTRODUCTION BY H. A. SNELLEN, M.D.

LEYDEN, HOLLAND

IN VIEW of the far-reaching consequences of the recently developed methods of surgical correction in cases of pulmonary and mitral stenosis, the formula of Gorlin and Gorlin[1] has offered valuable and much needed aid in selecting patients for these operations, as it provides a way of calculating the valvular area. A much simpler formula, however, based on Poiseuille's law and intended to be used for an approximate estimate of the degree of the stenosis by calculating "valvular resistance" has been given by Silber and associates[2] and by Dow and associates.[3] One might be tempted to prefer the latter both because of its simplicity and also because of a natural mistrust in using an apparently overexact calculation for a complicated biologic problem.

For these reasons it was thought worth while to study the problem more fully from a theoretical point of view, although Gorlin and Gorlin have obtained satisfactory confirmative evidence in six autopsied cases and five operated cases of mitral stenosis. It was particularly hoped that the constant of Gorlin and Gorlin's formula could be calculated theoretically and that in this way the accuracy of the method could be estimated.

The following paper, which was read at a meeting of the cardiology section of the Dutch Biophysical Society in Utrecht, has therefore a twofold purpose: first, to compare the merits of Gorlin and Gorlin's formula for measuring the valve area with those of the Poiseuille formula for estimating the valvular resistance (or "stenotic index" of Silber and associates) and, second, to investigate the accuracy and reliability of Gorlin and Gorlin's method from a theoretical standpoint.

From the Center of Cardiovascular Studies, University Hospital, Leyden.

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It will be shown that the use of the Poiseuille formula is not warranted because the blood flow through the valves is in all probability not of a laminary nature. Moreover, the term "resistance" should not be used in this connection because this term implies a direct correlation of the flow with pressure gradient, whereas in valvular stenosis the pressure gradient will be shown to vary with the square of the flow. This means that if one calculates the resistance of the valves in the usual way, that is, by dividing pressure gradient by flow, one does not obtain a constant which is characteristic for the valves which are examined, but a term which still varies with the flow through the valves and, therefore, is worthless in defining the physical properties of these apertures. The most important clinical consequences of this variation of valvular impediment to blood flow with changes in the blood flow itself are, of course, seen in cases which possess an alternative route for the blood stream as occurs with tetralogy of Fallot. In pure pulmonary stenosis a rise of right ventricular pressure may be observed in response to slight exertion or to emotional stimuli, which is caused or at least aggravated by the same mechanism and which may be also of clinical significance in some circumstances. The rapid rise of pulmonary pressure during exercise in mitral stenosis can be explained in the same way.

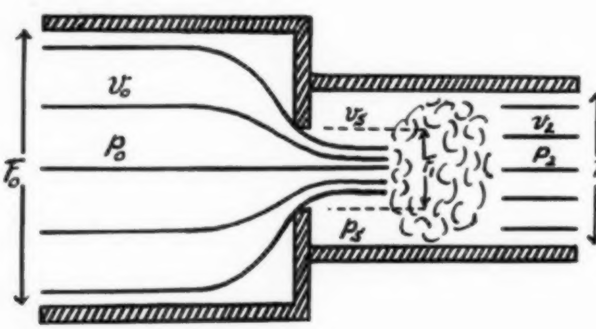

Fig. 1.

F_0 = area of the "vessel" proximal to the valves
F_1 = area of the valves
F_2 = area of the "vessel" distal to the valves
V_0 = velocity in the "vessel" proximal to the valves
V_s = velocity immediately after the valves
V_2 = velocity in the "vessel" distal to the valves
p_0 = pressure in the "vessel" proximal to the valves
p_s = pressure immediately after the valves
p_2 = pressure in the "vessel" distal to the valves

On the other hand, the formula given by Gorlin and Gorlin appears to be a satisfactory approximation of the problem for, although the constant of this formula is not, strictly speaking, a true constant figure, it may be regarded as such for all practical purposes and its value as determined by the authors mentioned was found to coincide rather closely with the result reached by theoretical deduction.

DISCUSSION OF THE PROBLEM

Any attempt to answer the questions put forward in the Introduction must be based on the deduction of a mathematical formula, which describes the phenomena occurring in the neighborhood of heart valves. In a given case, however, it is impossible to know all the details, such as the topographic proportions and the distribution of the blood stream, necessary for an exact calculation. Therefore, one has to be satisfied with an approximate method, which makes use of a schematic model of the heart valves and their neighborhood (Fig. 1). One can deduce a mathematical description for this model using known hydrodynamic formulas,[4] if some suppositions for simplification are introduced. In the ensuing discussion these suppositions and the equation derived from them will be dealt with first (I) (the mathematical deduction will be given separately in the Appendix), followed by the conclusions to be drawn from the equation mentioned (II) and the rationale (III) for the suppositions listed under Part I. Subsequently, the application of these conclusions (drawn in Part II) to clinical problems will be discussed (IV), and our results will be compared with those of Gorlin and Gorlin (V).

I. *The suppositions* are:

A. That the volume of blood flow is constant.

B. That the influence of the viscosity of the blood during its passage through the opening of the valves is negligible.

C. That the viscosity causes turbulence distal to the orifice, through which a pressure decrease originates, which is independent of the magnitude of the viscosity within wide limits.

For the schematic model based on the suppositions mentioned above the following equation holds true, which will be deduced in the Appendix:

$$p_o - p_2 = \frac{\rho i^2}{2\,F_1^2} \times \frac{1}{(\alpha\,\varphi)^2} \quad \text{.................. Equation 10}$$

p_o is the pressure proximal to the valves and p_2 the pressure distal to the valves; ρ is the density of the blood, and i the volume of flow. F_1 is the area of the orifice, α is a constant, which depends on the shape of the valves, and φ is a factor, which depends on α, the area of the diameter of the vessel proximal to the valves (F_o), the area of the diameter of the vessel distal to the valves (F_2) and F_1 (see Appendix: Equation 9b).

II. *Some conclusions* can be made from Equation 10:

A. The pressure difference ($p_o - p_2$) is proportional to the square of the volume of flow (i^2). This is quite different from the conditions in a cylindrical tube, in which the pressure difference is directly proportional to the volume of flow. In the latter case the constant ratio between ($p_o - p_2$) and i is called resistance, which is a generally accepted definition. In connection with the schematic model of the heart valves, however, it is not permissible to use the term "resistance" for the ratio between ($p_o - p_2$) and i is not constant, but is dependent on i.

B. The constant value of F_1 can be calculated, if ($p_o - p_2$) and i are determined, supposing $\alpha\,\varphi$ to be known.

C. The product $\alpha\,\varphi$ is not a constant, but depends on the shape of the valves, the vessels proximal and distal to the orifice and the magnitude of the orifice.

$\alpha\,\varphi$ can be calculated for any given situation. Under certain conditions, however, this factor may be considered constant as will be discussed under Part IV.

D. If the conditions are such that $\alpha\,\varphi$ may be considered constant, Equation 10, valid for the schematic model, is identical with the formula of Gorlin and Gorlin, which is to be discussed in Part V, and which has been found by the authors mentioned to hold true in vivo. We can add to this the fact that in the Leyden Cardiology Department a similar satisfactory agreement was found between the estimated size of the mitral orifice at operation and the surface calculated by the method of Gorlin and Gorlin. Moreover, calculations of the mitral orifice from the findings at rest and during exertion gave virtually identical results.

III. *In order for Equation 10 to be valid* not only for the model but also for the living heart, it is necessary that the suppositions used for deducing the formula are compatible with the situation in vivo.

A. "The volume of blood flow is constant." This supposition is surely not in accordance with the biologic facts; the formula, therefore, does not seem to apply to the problem in question, but if the formula is valid at any moment of the heart beat, one may use it in vivo as well.

It is evident that the fluctuating pressure difference resulting from the heart beat will cause a fluctuating volume of flow. The inertia of the blood, however, causes a delay in the adaptation of the volume of flow to changes in pressure difference. Thus a term will have to be inserted into the formula, which represents this delay. One can show, however, that the time delay may be considered to be short when compared with the interval during which the valves are open; consequently, the influence of the inertia may be neglected (see Appendix). Equation 10 is thus a good approximation at any moment of the heart beat and therefore is also valid when using mean values of the pressure difference and the volume of flow during the time the valves are open. The last point will be discussed in more detail in Part IV.

B. "The influence of viscosity of the blood during its passage through the opening of the valves is negligible."

This supposition is also a good approximation, which follows from a brief calculation (see Appendix). Taking into account the thickness of the valves, the volume of flow in the opening, the viscosity and the density of the blood, it is clear that the influence of the viscosity may be neglected and the blood in the opening may be considered "frictionless." In the absence of friction effects including turbulence (see Appendix), no energy loss occurs in the opening itself.

C. "The viscosity causes turbulence distal to the orifice, through which a pressure decrease originates, which is independent of the magnitude of the viscosity within wide limits."

The blood coming through the opening will mix with the stagnant blood in the vessel distal to the valves. This results in an energy loss, which causes a pressure decrease. Theoretically this fall in pressure is only dependent on the velocity of the blood in the opening and the velocity in the vessel distal to the orifice, and not on the magnitude of the viscosity; this is checked by many experiments.[4]

IV. *Since the schematic model and the suppositions* on which it is based are good approximations of the situation in vivo, Equation 10 and the conclusions under Part II may be used to answer the questions posed in the Introduction.

A. Is it allowed to use the resistance formula of Poiseuille for estimating the degree of stenosis? The answer must be in the negative, because this formula is valid for a fluid flowing in a laminar way because of its viscosity, and it is shown that the fluid passing through a heart valve can be considered to possess no viscosity.

The inadvisability of using the Poiseuille formula for calculating resistance in the case of valvular flow can also be shown in another way. One could try to use the simplified resistance formula, which commonly is designated as Poiseuille's formula, as a device for estimating the degree of stenosis ("stenotic index" of Silber and associates). In the formula:

$$R = \frac{p_o - p_2}{i} \quad \text{.......... Equation 14}$$

the value of $p_o - p_2$ from Equation 10 has to be substituted:

$$R = \frac{\rho i}{2\, F_1^2} \times \frac{1}{(\alpha\, \varphi)^2} \quad \text{.......... Equation 15}$$

From Equation 15 one finds that the "stenotic index" obtained in this manner is proportional to the volume of the stream, that is, with every change in the minute volume one obtains a different "stenotic index" and this, therefore, is of no value.

B. From Equation 10 one may calculate the constant value (F_1) for any given orifice; hence, the formula given by Gorlin and Gorlin, which is in principle identical with our Equation 10, offers a practical determination of the degree of stenosis. The value for F_1 is:

$$F_1 = \frac{i}{\alpha\varphi\sqrt{\dfrac{2(p_o - p_2)}{\rho}}} \quad \text{.......... Equation 16a}$$

C. What is the degree of accuracy of this method? Errors in determining i, p_o, and p_2 will be discounted, although they may give an error of 5 to 10 per cent for F_1.

From a theoretical point of view, however, two points will be discussed:

1. Formula 16a is valid for the relationship between volume of flow and the pressure difference at any given moment. In practice, however, one determines the mean values of these factors.

2. $\alpha\varphi$ is an unknown and inconstant factor, which is dependent on F_o, F_1, and F_2.

The difficulty named under 1. would not exist if one were to calculate the mean square root of the pressure difference, as well as the mean volume of flow; but actually the square root of the mean pressure difference is calculated and this introduces an error. Is the magnitude of this error so great that one has to change to the more laborious, accurate method? It is obvious that, while the estimation of pressure difference at any moment in all cases is difficult, it is generally impossible to do so in the case of the mitral valves, unless one was to do an arterial catheterization simultaneously in order to measure the left ventricular and arterial pressures directly. By employing both methods of calculation with the help of pressure curves taken in our hospital, it becomes evident that the error of the method in use is less than 5 per cent. It is of the same

magnitude as that found on determining i, p_o, and p_2, being less than the error resulting from the unknown factor mentioned in 2. It is therefore possible to continue the current practice of calculation.

In the discussion of 2. it is first necessary to outline the details of the relationships of $\alpha\varphi$ resulting from Equation 9b (see Appendix), which is as follows:

$$\alpha\,\varphi = \frac{\alpha}{\sqrt{1 - \left(\frac{\alpha F_1}{F_o}\right)^2 - 2\,\frac{\alpha F_1}{F_2}\left(1 - \frac{\alpha F_1}{F_2}\right)}} \quad \text{.....Equation 17}$$

The point must be made, however, that α is also a function of $\frac{F_1}{F_o}$, but that if $\frac{F_1}{F_o}$ is less than 0.2, α is almost constant. As this region is of the greatest importance α will be considered to be constant in the following remarks. In order to obtain an impression of the value of $\alpha\varphi$, a graph has been made (Fig. 2) in which $\alpha\varphi$ has been plotted against $\frac{F_1}{F_o}$ for two values of α and three of $\frac{F_2}{F_o}$. It is clear from the graph that $\alpha\varphi$, with an accuracy of 10 per cent, can be considered as independent of $\frac{F_2}{F_o}$, provided $\frac{F_1}{F_o}$ is less than 0.1, that is, to the left of the dotted line. One can say, with a similar degree of accuracy, that $\alpha\varphi$ is independent of $\frac{F_1}{F_o}$. On determining the mean values for $\alpha\varphi$ for all values of α, provided $\frac{F_1}{F_o}$ is 0.05, one obtains the dependence of the first magnitude on α with an error of about 10 per cent. With a fixed value for α in any given valve, $\alpha\varphi$ is a constant with the error as mentioned, provided $\frac{F_1}{F_o}$ is less than 0.1. The latter restriction causes no difficulty, for it is our intention to calculate the area of stenosis and thus to determine the area of small orifices as accurately as possible. When the areas concerned are large, their accurate determination becomes uninteresting from a surgical point of view.

By choosing a constant $\alpha\varphi$ it becomes possible to calculate the area of a stenosis to an accuracy of 10 per cent, whereas for a normal opening too high a value is obtained. The condition, however, is that α is known for the opening concerned.

This latter provides us with our greatest difficulty, for α cannot be measured. We are able to estimate the magnitude of α for the different valves from the average size of anatomic specimens, but it must be borne in mind that large individual variations occur. With the values estimated for α, the error will usually not be greater than 20 per cent; due to individual variation this error may increase to as high as 40 per cent.

At the point of stenosis of the pulmonary and aortic valves a circular opening is generally present, while the cavity proximal to this opening is conical in shape. In both cases the shape of the vessel is nearly that of Fig. 3 and one may expect that α will be nearly 1.0; one may estimate it to be 0.8 to 0.9, so that the constant value of $\alpha\varphi$ can be considered to be 0.9 to 1.0 (see Fig. 2).

The stenosis of the mitral and tricuspid valves are oval or slit shaped and, moreover, their margins are often made irregular by the local deposit of calcium salts. Hence, although the shape of the vessel is also conical, one is unable to say that its shape is like Fig. 3. One may expect, therefore, that α is 0.5 to 0.6, and thus the constant value of $\alpha\varphi$ is 0.6 to 0.7.

Gorlin and Gorlin have also attempted to use this formula to help determine the magnitude of abnormal intracardiac openings, but it is clear from the foregoing that this will only be effective in the case of a small connection. When the abnormal openings are large the method gives exagger-

ated results, which are dependent on $\frac{F_1}{F_o}$ and $\frac{F_2}{F_o}$, the ratios of which are unknown. Presupposing that this is borne in mind the use of the formula can provide us with valuable information.

The shape of a patent ductus arteriosus can be compared with Fig. 3; so that $\alpha\varphi$ can again be considered to be 0.9 to 1.0.

In the case of a septal defect, either atrial or ventricular, the situation is probably like that drawn in Fig. 1, where the value 0.6 may be given for α, and $\alpha\varphi$ is about 0.65.

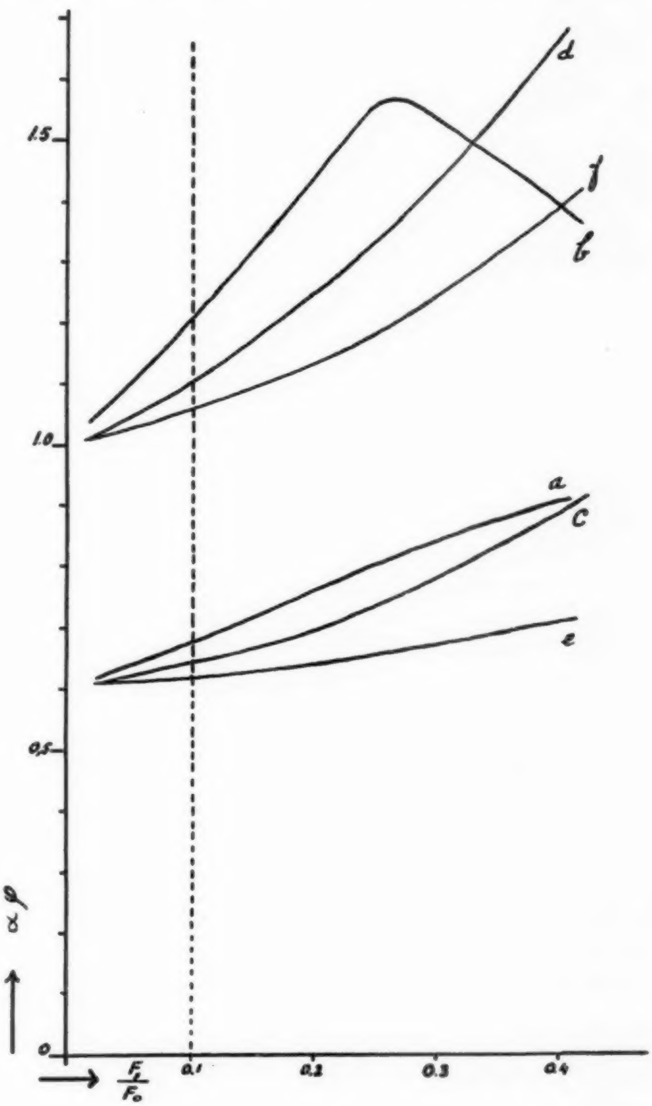

Fig. 2.

a: $F_2 = \frac{1}{2}F_o$	$\alpha = 0.6$	d: $F_2 = F_o$	$\alpha = 1.0$
b: $F_2 = \frac{1}{2}F_o$	$\alpha = 1.0$	e: $F_2 = 2F_o$	$\alpha = 0.6$
c: $F_2 = F_o$	$\alpha = 0.6$	f: $F_2 = 2F_o$	$\alpha = 1.0$

V. We are now in a position *to compare our theoretical deductions* with the results of Gorlin and Gorlin.

Using C.G.S. units in Formula 16a, i is expressed in ml./sec.; $(p_o - p_2)$ in dynes/cm.[2]; ρ in Gm./ml.; and F_1 in cm.[2] Practically speaking, however, the pressure is generally expressed in mm.Hg $(p_o' - p_2')$. This requires the introduction of a conversion factor. If one also incorporates in this factor $\sqrt{\frac{2}{\rho}}$ one obtains the following formula:

$$F_1 = \frac{i}{\alpha\varphi \times 50.5 \sqrt{p_o' - p_2'}} \qquad \text{Equation 16b}$$

For comparison the formula of Gorlin and Gorlin is appended:

$$A = \frac{F}{C \times 44.5 \sqrt{P_1 - P_2}} \qquad \text{Equation 16c}$$

where $A = F_1$
$F = i$
$P_1 = p_o'$
and $P_2 = p_2'$

$$\therefore \alpha\varphi \times 50.5 = C \times 44.5 \qquad \text{Equation 18a}$$

or $$\alpha\varphi = \frac{C}{1.14} \qquad \text{Equation 18b}$$

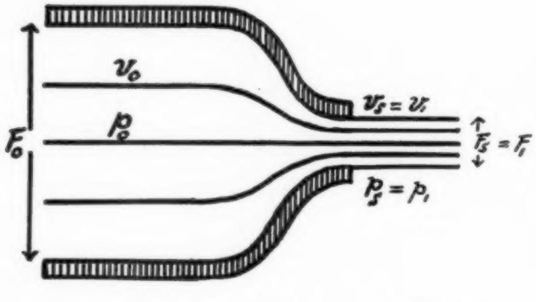

Fig. 3.—For explanation see legend to Fig. 1.

C has been calculated empirically for some defects by these authors. In mitral stenosis they found C to equal 0.7; from Equation 18b $\alpha\varphi$ is found to be 0.61. In pulmonary stenosis C has been determined as 1.0, and $\alpha\varphi$ deduced as being 0.88. Similar numbers have been found for cases of patent ductus arteriosus.

When these empirical values are compared with the values computed above, they are found to be in agreement.

In their publication Gorlin and Gorlin deal with results accruing from the use of the formula with data obtained from the patient both at rest and on exertion. In some cases of mitral stenosis, they also give the comparison of the areas calculated with the use of the empirical C with the values obtained at autopsy.

Both tables give the impression that, in general, the error lies within the limits computed theoretically.

SUMMARY

Two methods have been published so far to determine the necessity for surgical interference in cases of valvular stenosis.

1. The "resistance" of the valve has been determined by means of Poiseuille's formula, the result being sometimes termed the "stenotic index." It has been demonstrated theoretically that blood may be considered as a liquid with a negligible viscosity in the valve opening. As the flow is not laminar the formula for resistance becomes invalid, for in applying the formula the stenotic index is found to be directly proportional to the volume of flow. In other words, any change in the minute volume will give a change in the calculated "resistance."

2. The area of the ostium has been calculated by means of the formula of Gorlin and Gorlin. Although the "constant" used in this formula proves to be a variable term, by limiting its use to small orifices and allowing an error of 10 per cent, it may be considered, practically speaking, to be a constant: its value depending on the form of the orifice. The form of any given defect will vary with the individual. Generally speaking the acceptance of a constant provides an error of 20 per cent; when large individual deviations occur, this error may be as great as 40 per cent.

Anatomic data provide approximate evidence for the value of the constant in various defects.

Even for abnormal shunts the method may be useful, provided one bears in mind that exaggerated values are obtained when the opening is large. The "constant" may only be considered to be so when the orifice is small; failing this, the value of the "constant" is higher.

The empirical values for the constant of some defects, calculated by Gorlin and Gorlin, are compared with those obtained theoretically and are found to agree satisfactorily. Concerning the errors in practice we would refer the reader to the tables given by Gorlin and Gorlin.

APPENDIX

Bernouilli (1738) derived an equation for an "ideal" fluid, which velocity is constant at every point (Supposition A). An "ideal" fluid is defined as one which has no viscosity, although the formula is also valid, when the viscosity is low (Supposition B). His equation is of fundamental importance in certain hydrodynamic problems, when the viscosity exerts no influence.

This equation is:

$$p + \frac{\rho v^2}{2} = \text{Constant} \qquad \text{Equation 1}$$

which is of course an energy balance expression for all fluids under these conditions.

p = pressure = force per cm.^{2}

ρ = density = mass per ml.

v = velocity = the distance covered by a single particle of the fluid per second.

If we imagine a tube to be occluded by a diaphragm pierced by an orifice (Fig. 4) where the area of the tube is F_o and that of the orifice F_1, the velocity in the tube v_o and distal to the orifice v_s, the pressure in the tube p_o and distal to the orifice p_s, application of Equation 1 gives:

$$p_o + \frac{\rho v_o^2}{2} = p_s + \frac{\rho v_s^2}{2} \qquad \text{Equation 2}$$

Since the stream lines, which are represented by solid lines, are curved in the neighborhood of the orifice, the area of the issuing fluid jet, F_s, is less than F_1.

$$F_s = \alpha F_1 \qquad \text{Equation 3}$$

The contraction factor α depends on the form of the orifice; if the diaphragm is thin and if the hole is circular, α is about 0.6; on the other hand, if the vessel has a shape adopted to the type of flow (Fig. 3), α may approximate the value of 1.0.

The volume of the stream i (the volume of fluid, which passes along the tube per unit time) is the same, of course, both proximal and distal to the diaphragm.

$$i = F_o\, v_o = F_s\, v_s = \alpha F_1\, v_s \qquad \text{Equation 4a}$$

From Equations 2, 3, and 4a it follows:

$$p_o - p_s = \frac{\rho v_s^2}{2}\left[1 - \left(\frac{\alpha F_1}{F_o}\right)^2\right] \qquad \text{Equation 5}$$

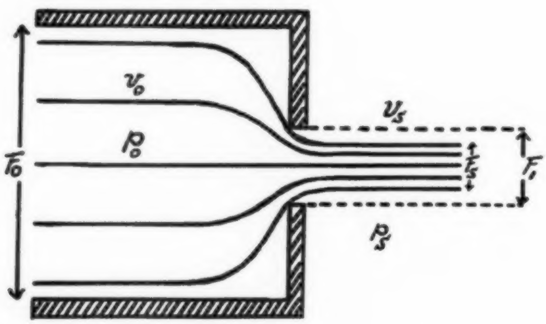

Fig. 4.—For explanation see legend to Fig. 1.

Distal to the diaphragm it is possible to insert a second tube (Fig. 1) with an area F_2, in which the velocity is v_2 and the pressure p_2.

The viscosity, which till this point has been considered negligible, must now be considered, for when there exists the least degree of viscosity, the fluid issuing from the orifice will mix with the stagnant fluid in the second tube (Supposition C). After mixing, the fluid will flow in such a manner that the velocity at each point on a cross-sectional area is about equal; with the assistance of the law of conservation of momentum the increase in pressure $p_2 - p_s$ can be calculated:

$$p_2 - p_s = \rho v_2\, (v_s - v_2) \qquad \text{Equation 6}$$

This pressure difference is thus independent of the viscosity of the fluid. It has been demonstrated experimentally[4] that Equation 6 is indeed valid, unless the viscosity becomes too great.

In the second tube the volume of the flow must be the same as in the first:

$$i = \alpha F_1\, v_s = F_2\, v_2 \qquad \text{Equation 7}$$

From Equations 6 and 7 one obtains:

$$p_2 - p_s = \frac{\rho v_s^2}{2} \times 2\,\frac{\alpha F_1}{F_2}\left(1 - \frac{\alpha F_1}{F_2}\right) \qquad \text{Equation 8}$$

Elimination of p_s from Equations 5 and 8 gives:

$$p_o - p_2 = \frac{\rho v_s^2}{2}\left[1 - \left(\frac{\alpha F_1}{F_o}\right)^2 - 2\,\frac{\alpha F_1}{F_2}\left(1 - \frac{\alpha F_1}{F_2}\right)\right] \text{..........Equation 9a}$$

For convenience on transposing $\frac{1}{\varphi^2}$ for:

$$\left[1 - \left(\frac{\alpha F_1}{F_o}\right)^2 - 2\,\frac{\alpha F_1}{F_2}\left(1 - \frac{\alpha F_1}{F_2}\right)\right] \text{..........Equation 9b}$$

one obtains:

$$p_o - p_2 = \frac{\rho v_s^2}{2} \times \frac{1}{\varphi^2} \text{..........Equation 9c}$$

From Equation 4a it follows:

$$v_s = \frac{i}{\alpha F_1} \text{..........Equation 4b}$$

which, substituted in Equation 9c, gives:

$$p_o - p_2 = \frac{\rho i^2}{2\ F_1^2} \times \frac{1}{(\alpha\varphi)^2} \text{..........Equation 10}$$

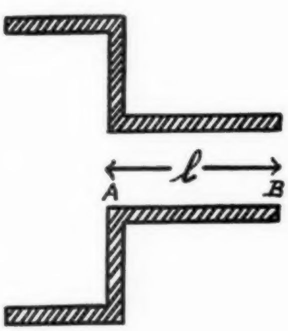

Fig. 5.

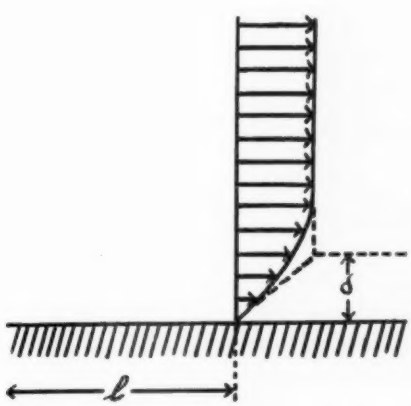

Fig. 6.

The suppositions, which are introduced for the purpose of deducing Equation 10, must now be discussed.

A. The volume of blood flow is not constant in vivo. What influence has this on the result obtained?

If a difference in pressure is effected between two points along a tube, it is some time before the velocity adapts itself to this pressure difference.

The time, (T) will depend on the velocity (v) and the length of the tube (l). A fair approximation is given by:

$$T = \frac{2\,l}{v} \text{..........Equation 11}$$

When one substitutes 0.5 cm. for l and 100 cm./sec. for v, one obtains the figure 0.01 second. For heart valves the thickness (l) is usually less than 0.5 cm. and v greater than 100 cm./sec., and hence, generally, the time (T) will be shorter than 0.01 second. As this time can be considered to

be short, when compared with the time that the valves are open, the effect may be neglected and the blood considered to follow immediately any change in pressure difference. Equation 10 holds at any given moment.

B. Is it permitted to neglect the viscosity of the blood as it passes the opening?

In a vessel with the form illustrated in Fig. 5 all liquid particles possess the same velocity at A since every particle has been subjected to the same pressure drop. Distal to A the particles nearest the wall will be slowed down by the friction occasioned there. This slowing will extend toward the middle of the tube as the distance from A increases. Fig. 6 shows the velocity distribution at B, a distance l from point A; δ is the distance over which the slowing has been effective; the rest of the fluid flows as if no friction were present. This distance (δ) can be calculated from the formula:

$$\delta \approx \sqrt{\frac{\eta l}{\rho v}} \quad \text{.......................Equation 12}$$

(η = viscosity)

When one substitutes 0.5 cm. for l and 100 cm./sec. for v, the mean value 1.04 Gm./ml. for ρ and 0.023 poise for η, one obtains a value of 0.01 cm. for δ. For the same reasons as given above, δ will generally be less than 0.01 cm. The calculated value is small when compared with the diameter of the orifice and for this reason this effect may also be neglected.

If one considers the possibility of the flow becoming turbulent within layer δ, one has to calculate the Reynolds number (Re).

$$Re = \frac{v\,\delta\rho}{\eta} \quad \text{.......................Equation 13}$$

With the above values the Reynolds number obtained is 45. The liquid will become turbulent, if Re is greater than about 2,000; it is clear, therefore, that the flow will not become turbulent even with v much higher than 100 cm./second.

C. This supposition does not call for further discussion.

It is clear from the foregoing that Equation 10 provides a satisfactory working approximation in the hydrodynamics of heart valves.

We wish to express our appreciation to Dr. R. M. Collister for her criticism and help during the preparation of the text of this publication.

REFERENCES

1. Gorlin, R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves, and Central Circulatory Shunts. I. Am. Heart J. **41**:1, 1951.
2. Silber, E. N., Prec, O., Grossmann, N., and Katz, L. N.: Dynamics of Isolated Pulmonary Stenosis, Am. J. Med. **10**:21, 1951.
3. Dow, J. W., Levine, H. D., Elkin, M., Haynes, F. W., Hellems, H. K., Whittenberger, J. W., Ferris, B. G., Goodale, W. T., Harvey, W. P., Eppinger, E. C., and Dexter, L.: Studies of Congenital Heart Disease. IV. Uncomplicated Pulmonic Stenosis, Circulation **1**:267, 1950.
4. Prandtl, L.: Strömungslehre, Vieweg, Braunschweig, 1949.

STUDIES IN MITRAL STENOSIS. IV.

The Relative Merits of Various Diagnostic Methods in Mitral Valvular Disease

G. Biörck, M.D., O. Axén, M.D., H. Krook, M.D., L. Andrén, M.D., and H. B. Wulff, M.D.

Malmö, Sweden

THE CLINICAL diagnosis of mitral regurgitation has long been regarded as difficult to establish. The single valuable sign generally agreed upon has been an apical systolic murmur, but the extensive misuse of this criterion in labeling various normal persons and patients suffering from other cardiac diseases with the diagnosis of mitral regurgitation or "insufficiency" has brought this diagnosis into a certain disrepute. It may also be maintained that most lesions of the mitral valve ring result in predominant stenosis and only rarely in predominant regurgitation, and that the effect of the stenosis is, clinically, the most important one. The interest in the diagnosis of mitral regurgitation has, therefore, been minimal in later years.

The introduction of surgical techniques for the relief of mitral stenosis,[1-8] which is now a routine procedure, and of mitral regurgitation, which is still in a somewhat experimental stage, has radically changed this situation. Thus, it is not only fundamental to make a correct diagnosis of the valvular lesion per se but, for the proper selection of patients for operation, it is likewise essential to estimate the relative importance of the stenotic and the regurgitant components of the disturbance to intracardiac hemodynamics which is caused by the valvular lesion. As already indicated, the clinical diagnosis of mitral stenosis of any pronounced degree rarely is difficult to the specialist, whereas an appreciation of the degree of regurgitation still meets with considerable difficulty.

Unfortunately, current medical teaching is not very helpful in the latter regard. From a perusal of some medical textbooks and monographs, the following statements may be quoted:

Mitral Insufficiency.—

"Signs: Systolic murmur, best heard at or just outside the region of the cardiac apex, either following or merging with the first heart sound and usually transmitted to the left axilla. Its quality may be blowing, harsh or musical, with relatively high pitch. A systolic thrill is occasionally palpable.

From the Departments of Medicine, Radiology, and Surgery, Allmänna Sjukhuset, Malmö, Sweden.
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"Enlargement of the heart may be slight and recognizable only on radiography, but without it deformity of the mitral valve should not be diagnosed."[9]

"There are no symptoms to be attributed usefully to mitral regurgitation. The only sign that can be named is a systolic murmur. . . . The sign of regurgitation is to be recognized as very variable from case to case, (and) is chiefly a guiding sign."[10]

"Mitral regurgitation due to valvular disease cannot be easily differentiated from mitral regurgitation due to ventricular dilatation except when it is combined with proof of mitral stenosis. (Given the auscultatory and/or roentgenologic findings of a mitral stenosis) the presence of an apical systolic murmur means mitral regurgitation as well as mitral stenosis and is due to valvular disease (provided a respiratory murmur can be excluded) . . . the degree of mitral regurgitation is indicated roughly by the intensity of the apical systolic murmur in that the murmur is loudest, other things being equal, when regurgitation is moderate, and faintest when the regurgitation is only very slight or else of extreme degree."[11]

"When a patient who suffered an attack of rheumatic fever displays an apical systolic murmur of grade II or louder intensity a year or more later, one is warranted in making a diagnosis of organic mitral insufficiency, if there is no other explanation for the murmur. . . . (When in mitral stenosis) a significant apical systolic murmur is present, one should make the additional diagnosis of mitral insufficiency."[12]

". . . its diagnosis is more speculative. An apical systolic murmur is often present in patients who also exhibit the characteristic diastolic murmur of mitral stenosis. There is no evidence that, in these cases, the associated mitral incompetence adds to the gravity of the prognosis."[13]

"Qu'il s'agisse d'insuffisance valvulaire ou myocardique, le souffle systolique est attribué suivant la conception classique à la régurgitation du sang du ventricle gauche dans l'oreilette au moment de la systole. Le mécanisme seul de la fuite varie. Quant au souffle: il est dû à la production a'une veine fluide à travers un orifice rétréci par mise en vibration de l'orifice et de la paroi sur laquelle se brise cette veine fluide. En fait, l'intensité du souffle et sa durée est moins liée au volume du débit qu'à l'étroitesse de l'orifice de fuite et à la persistance de cette fuite jus qu'à la fin de systole."[14]

"The clinical detection of mitral regurgitation in the presence of stenosis is at best difficult."[34]

The apparent difficulty in the diagnosis of mitral regurgitation has also led to great differences of opinion concerning its prognosis. White[11] maintains that marked mitral regurgitation means a greater strain on the heart than does mitral stenosis with shorter life expectancy, while Svartz and Ernberg,[15] in studying material of a hospitalized case clinically diagnosed as mitral regurgitation, observed a very favorable prognosis. Reasonably, such differences reflect equally different criteria for the diagnosis.

In later years, the possibilities of surgical therapy of certain congenital malformations of the heart as well as recently of mitral stenosis has raised the interest in employment of several elaborate methods for the study of cardiac and intracardiac conditions. Such methods are cardiac catheterization, angiocardiography, electrokymography, and ballistocardiography. Furthermore, the use of several unipolar chest leads and extremity leads in electrocardiography has given more detailed information on the position of the heart and of hypertrophy of the left or right ventricular myocardium. Phonocardiography has likewise aided in the control and evaluation of auscultatory findings. We have tried to collect data on patients with mitral valvular disease, referred to us for study with regard to possible surgical treatment, with the use of as many of these diagnostic methods as possible. Employing hitherto-accepted criteria, we have attempted, in each of these methods, to arrive at a final judgment considering the relative preponderance of mitral stenosis and regurgitation, respectively. These judgments were then compared to each other.

METHODS

The differentiation between predominant mitral stenosis and predominant mitral regurgitation must be made with regard to their different effects upon cardiopulmonary hemodynamics. Thus, it may be assumed that in stenosis the left auricle will be distended and the left ventricle, which receives a strangulated blood flow, correspondingly small. In mitral regurgitation, the left ventricle, as well as the left auricle, will receive a normal or even an increased blood flow and will, therefore, be normal or increased in size. The effective (aortic) cardiac output may vary from case to case, depending upon pressure relationships, but is generally low. In mitral regurgitation this does not mean that the total left ventricular output is low. Pure mitral stenosis may thus be diagnosed when there is a distention of the left auricle without an increase in size of the left ventricle, when the ventricular diastolic filling is accompanied by the typical stenotic murmurs, and when, in patients with regular heart rhythm, a pathologic increase in left auricular and pulmonary venous pressure is seen in auricular systole. The slow passage of blood through the stenotic valve will also result in a slow passage of blood through the whole of the lesser circulation. In mitral regurgitation, on the other hand, the left auricle will be enlarged as a result of double filling in ventricular systole, namely, both by the pulmonary veins and by the regurgitant blood flow from the left ventricle. In its attempt to secure an adequate aortic output despite the leak, the left ventricle will also increase in size in the same way as it does in aortic insufficiency. The backward jet in ventricular systole will cause a systolic murmur and a systolic pressure wave in the auricle and in the pulmonary veins. The passage of blood through the lesser circulation will not necessarily be delayed, but the entire left heart may serve as a pool, which empties itself slowly and incompletely. The main points of differentiation (Fig. 1) should be: (a) the left ventricular size, (b) the murmurs at the mitral orifice, (c) the pressure and volume changes within the left auricle and the pulmonary veins, and (d) the type of blood passage through the pulmonary circulation and the left heart.

Regarding *left ventricular size* (a), this may be studied by means of percussion of the left border of the heart and palpation of the apex beat, by unipolar chest lead electrocardiography, by chest roentgenography and by angiocardiography. Furthermore, operation (and autopsy) may confirm the previous observations. The *murmurs at the mitral orifice* (b) may be studied by means of palpation of thrills and auscultation, and the findings may be verified by phonocardiography. *Pressure and volume changes in the left auricle and the pulmonary veins* (c) may be studied by cardiac catheterization (so-called pulmonary capillary venous tracings, "pcv" curves) and by electrokymography. They may also be observed during operation. Finally, *the passage of blood through the lesser circulation and the left heart* (d) may be studied by determining the circulation time and, in particular, by angiocardiography.* It was also believed that ballistocardiography might give some information on the type of cardiac output.

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*Angiocardiography was first used in an attempt to discover large thrombi in the left auricle and to predict the size of the auricular appendage. It soon was found more useful for the study of left heart hemodynamics. This does not necessarily imply that thrombi cannot be detected by means of angiocardiography but only that we have not encountered such thrombi in our present material.

Few of these methods are without disadvantages and limitations. A differentiation of right and/or left ventricular enlargement is almost impossible in many instances, both on percussion and by ordinary roentgenography of the heart. The apex beat may be hidden behind a rib and thus difficult to evaluate. Even when felt, it is sometimes difficult to say what part the right ventricle plays. In aortic incompetence and hypertension a forceful apex beat may not mean mitral regurgitation at all. As for auscultation, the quotations earlier in this paper clearly show the state of the matter. However, up to present time teaching has not had access to in vivo control of the auscultatory findings, the criteria for diagnosis, therefore, being chiefly based upon post-mortem findings and seemingly logical explanations. One of the important duties of today's research in this field is to present the physiologic equivalents of the signs found at physical examination, thereby controlling and correcting the interpretation of bedside observations.

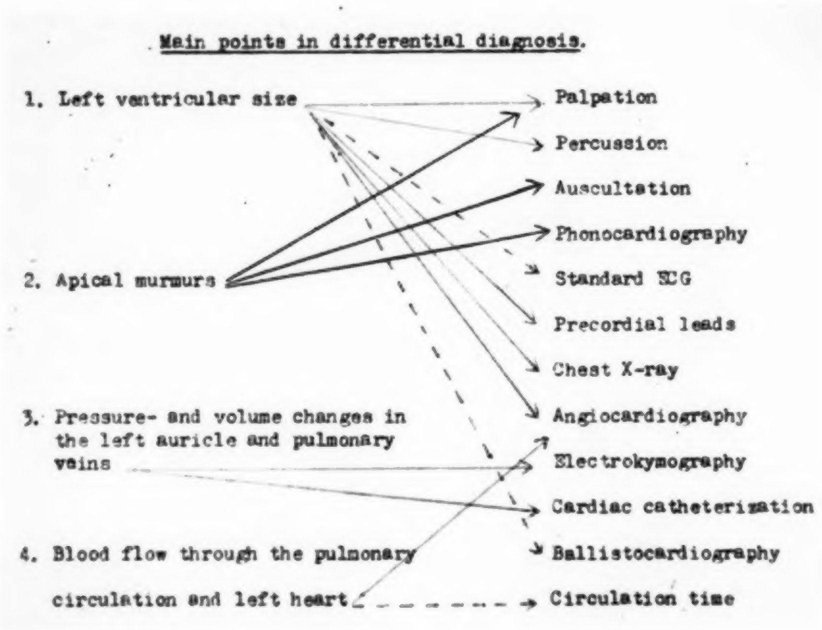


Fig. 1.

We have the impression that normal unipolar chest leads may occur also in ventricular hypertrophy, but hypertrophy demonstrated in such leads seems to give valuable information. The electrical axis, when definitely shifted to the right, is possibly consistent with predominant mitral stenosis, but in cases with normal electrical axis no conclusions are probably allowed. As already mentioned, the roentgenogram of the heart may be difficult to interpret in terms of ventricular hypertrophy. This applies not only to the delimitation of the right and left ventricle, but also to the image of the left ventricle in the frontal and the sagittal views.

Inasmuch as left auricular behavior is grossly disturbed in auricular fibrillation, proper information is difficult or impossible to obtain by means of electrokymography and so-called pcv tracings at cardiac catheterization, and the same applies to ballistocardiography because of the great variations in left ventricular filling in fibrillation. The size of the left ventricle is of doubtful value for the differentiation in question in patients with hypertension or any notable degree of aortic valvular lesion. This applies both to the determination of the apex beat, the roentgenologic images, and the electrocardiogram. The success of angiocardiography, finally, depends on a correct prediction of the time intervals of the events to be recorded, which has sometimes proved difficult.

Technical Details.—

Auscultation was generally performed by the same person (G. B.), and notes were taken on the character of sounds and murmurs in at least five places, namely, aortic and pulmonary areas, third-fourth intercostal space to the left of the sternum, at the apex and at the axilla. Systolic murmurs were graded according to Levine.[12]

Phonocardiograms were recorded from the places indicated above. The apparatus used was the phonocardiograph type RC 5 connected to an electrocardiograph type Klinik, both manufactured by the Elema Company, Stockholm, Sweden. The phonocardiograms obtained by the six different channels record frequencies between 5 to 600 periods per second. In addition one electrocardiographic lead is recorded.

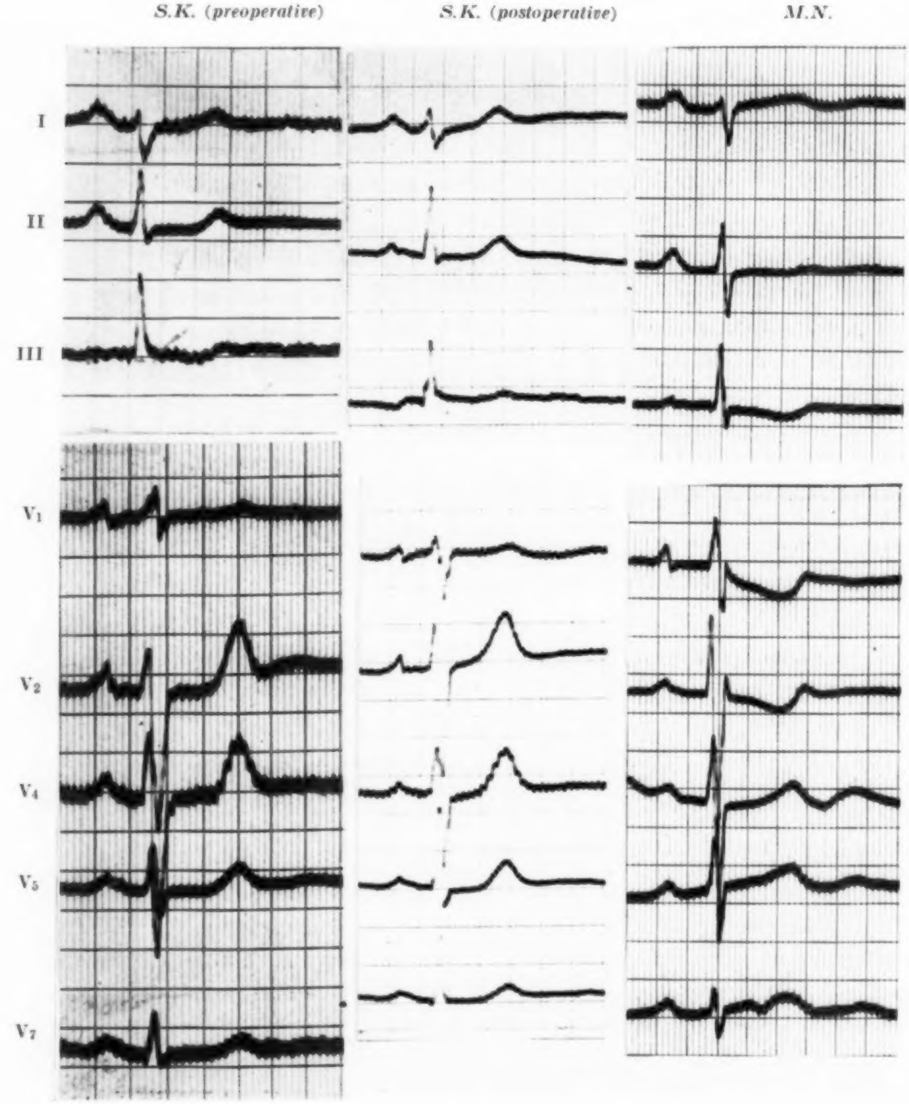
Electrocardiograms were recorded by the same Elema Klinik apparatus. Standard extremity leads, unipolar extremity leads according to Wilson, and unipolar chest leads V_1 to V_7 were registered, and in most instances also right-sided chest leads.

Roentgenography of the heart: The configuration of the heart and its chambers as well as of the degree of pulmonary vascularization was studied. In addition, heart volume determinations according to Liljestrand and associates[15] and Jonsell[17] were performed routinely.

Angiocardiography in cases of mitral stenoses was initially carried out in order to study the size and shape of the left auricular appendage and to reveal the presence of thrombi. Afterwards this method of investigation became particularly valuable for an exact determination of the enlargement of the left auricle with secondary deformation of the right auricle and ventricle, and, still more, for an exact representation of the left ventricle and the degree of mitral regurgitation.

The examination was performed under general anesthesia (intravenous Narkotal, Astra Co., Sweden) with oxygen apnea at the time of exposure. The contrast medium was 70 per cent Umbradil (Astra). A preliminary intravenous injection of 1 to 2 ml. of the contrast medium was made in all instances to test the iodine sensitivity of the patient. The amount of contrast medium in adults was always 50 ml., injected as rapidly as possible. The examination was performed by means of a special angiocardiography table, designed by Axén,[18,19] with simultaneous exposures in two planes at right angles. The patient was placed on the back

so that one frontal and one sagittal picture were obtained. Two sets of films were exposed every second. In consideration of the prolonged circulation time of these patients, eight to ten exposures were made immediately after the injection



A.

Figs. 2*A* and 2*B*.—Electrocardiograms from six of the patients in Table I. The tracings from Patient S. K. are pre- and postoperative ones, illustrating the tendency to leftward axis shift. Patients A. Ld, B. B., and E. M. are considered as having preponderant mitral regurgitation, while pure mitral stenosis was found in Patients S. K., M. N., and E. R.

of the contrast medium, after which there was a pause, calculated from the determination of the circulation time so that the contrast had reached the left heart before the serial exposures were continued. Electrocardiograms were

recorded during the examination. The moments of exposure were indicated on the electrocardiogram to enable an exact determination of the location of every pair of photographs in the cardiac cycle. All the patients examined tolerated the

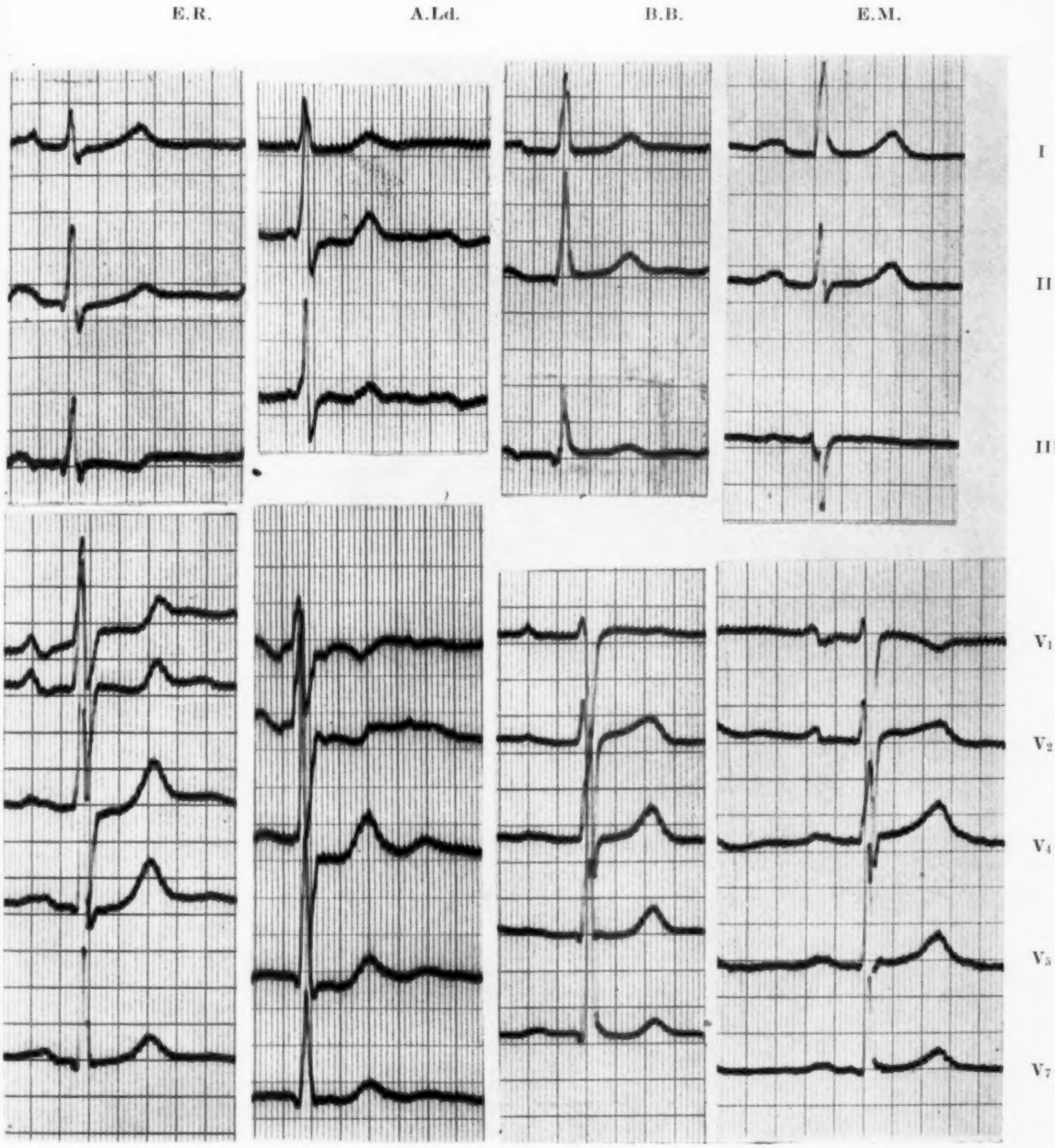


Fig. 2 *B.* *(For legend see opposite page.)*

examination well. Only one patient showed slight signs of pulmonary edema in connection with the anesthesia. Although cardiac catheterization had to be interrupted in this patient because of pulmonary edema, the angiocardiography could be accomplished without further complications.

TABLE I.*

PATIENTS	AGE (YRS.)	APEX BEAT	MURMURS	ELECTROCARDIOGRAPHY		ROENTGENOGRAPHY	ANGIOCARDIOGRAPHY	ELECTROKYMOGRAPHY	CARDIAC CATHETERIZATION	OPERATION	AUTOPSY	BLOOD PRESSURE (mm. Hg)	RHYTHM
				ELECTRICAL AXIS	VENTRICULAR HYPERTROPHY								
S. N.	24	0	Si	R	R	S	0	—	0	S		115/85	R
R. H.	35	0	S	R	R	S	S	—	0	S		120/90	R
M. N.	26	I	S	N/R	0	I	S	—	i	S		115/65	F
E. S.	52	S	S	R	R	S	—	Si	0	S	S	115/80	R
E. B.	44	S	S	R	r	Si	S	S	sI	S		125/75	R
E. R.	41	S	S	N	RL	S	—	SI	Si	S		120/85	R
A. P.	41	0	S	N	(r)	Si	—	S	Si	S		115/70	R
V. L.	33	S	S	N	(r)	S	—	0	S	S		120/75	R
M. Ö.	35	S	S	N	r	SI	S	Si	Si	S		120/60	R
S. H.	28	Si	S(i)	R	0	S	S	0	0	S		115/60	R
H. N.	44	S	S	N	1	S	S	—	0	Si	S	200/135	F
A. A.	37	I	SI	N	1	SI	—	—	0	SI	SI?	120/90	F
R. A.	31	I	S	R	0	S	S	(SI)	SI	S		100/50	R
A. Ld.	40	0	Si	N	(r)1	S(I?)	S(I?)	—	I	I		160/110	F
M. V. N.	37	S	S	R	R	S	S	S(i)	I	S		100/70	R
G. K.	39	0	SI	N	0	Si	Si	0	I	sI		100/60	F
A. Ln.	45	S	S	N	0	Si	S	—	0	S		130/90	F
S. A.	44	S	Si	N	(r)	Si	—	Si?	S	—		140/90	R
Hj. L.	49	I	SI	R	R	S	S	—	I	—		120/80	F
E. M.	31	0	I	L	1	S	I	SI	Si	—		130/75	R
S. J.	36	S	S(i)	R	r	S	—	S	0	—		130/85	R
B. B.	16	I	sI	N	1	I?	I	I	0	—		140/80	R
U. R.	21	I	sI	N	0	SI	—	(s)	0	—		120/70	R
M. W.	37	S	S	N	0	S	—	Si	S	—		130/70	R
M. L. O.	31	S	S	N	0	S	—	S	0	—		125/85	R

(For legend see opposite page.)

Electrokymography was performed with the use of Schönander's electrokymograph. Recording of the electrokymogram together with the electrocardiogram was made on the Elema Triplex outfit. Curves were obtained from several points of the silhouette of the left auricle, in conformity with standard technique.[20,21]

Cardiac catheterization was performed in the usual manner with No. 7-8 catheter. The catheter was placed in position for "pulmonary capillary venous" tracings (pcv) and then withdrawn to the pulmonary artery, right ventricle, and right auricle. Pressure recordings were obtained by means of the Tybjerg Hansen-Warburg manometer[23,33] connected to an Elema Klinik electrocardiograph. Blood samples were taken in the pcv position, in the right ventricle or the pulmonary

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*Table I is made up to show the differentiation of mitral stenosis and mitral regurgitation. At every examination, the responsible physician was asked to denote his evaluation of the degree of mitral stenosis or regurgitation in the individual case. Pure stenosis was denoted S, pure regurgitation I, and intermediate forms SI, Si and sI, depending upon the relative preponderance of the one or the other lesion. The following criteria were employed in Table I:

Apex beat.—Forceful = I, weak = S, and noninformative = O.

Murmurs.—Definite presystolic or mid-diastolic apical murmur = S, or, in cases with marked regurgitation, s. Systolic murmurs of Grade III to V = I or, in some cases with marked stenosis, i.

Electrocardiography.—Electric axis and ventricular hypertrophy in unipolar chest leads were noted. No definite conclusions as to the type of mitral valvular lesion seem to be justified with regard to the electrocardiogram. Pure mitral stenosis may, apparently, go with normal electric axis, whereas right axis shift probably is an unusual finding in mitral regurgitation. Left ventricular hypertrophy in unipolar chest leads should, in the absence of hypertension or aortic valvular disease, make one suspect mitral regurgitation. In the absence of marked right-sided heart failure, right ventricular hypertrophy is probably more common in mitral stenosis. For these reasons electric axis and ventricular hypertrophy are only denoted N = normal, L = left, and R = right, or, if the features are less well marked, l = left and r = right. The interpretation of the findings in terms of stenosis and regurgitation was left open, but it was felt that the presence of R's in both columns of the table strongly pointed to predominant stenosis.

Roentgenography.—Pronounced bulging of the left auricle without left ventricular enlargement = S. Enlargement of left ventricle in the absence of hypertension or aortic lesions = I or i.

Angiocardiography.—Marked enlargement of the left auricle with slow contrast passage into the left ventricle but normal emptying = S. Enlargement of the left auricle with less delayed filling of the left ventricle, causing an almost equal contrast density in both auricle and ventricle and impaired aortic output, signifying a partial reflux from the ventricle to the auricle = I or i. A dash denotes that no angiocardiography was performed.

Electrokymography.—The interpretation of the electrokymograms was cautious. The degree of mitral stenosis was graded according to the magnitude of the persisting auricular distention in diastole and of the auricular contraction. The degree of regurgitation has been evaluated with regard to the early phase of auricular filling and the moment of maximal filling during ventricular systole. We hesitate to draw any conclusions in patients with auricular fibrillation.

Cardiac Catheterization.—The pcv tracings were studied with regard to the type of presystolic and systolic waves. Marked presystolic waves were considered typical of stenosis and denoted S or s; marked systolic waves were denoted I or i. In some instances no satisfactory pcv tracings were obtained; these were denoted O. The significance of pcv tracings in auricular fibrillation must be judged with great caution.

Ballistocardiography.—No definite conclusions could here be drawn. However, some postoperative tracings show, in comparison with the preoperative ones, a return to a more normal picture, in particular, return of the H-I segment. No attempts were made to evaluate the tracings in terms of stenosis or regurgitation, and the findings with this method will not be further discussed in this paper.

TABLE II.

	APEX BEAT		MURMURS		ELECTROCARDIOGRAM				ROENTGENOGRAPHY		ANGIOCARDIOGRAPHY		ELECTROKYMOGRAPHY		CATHETERIZATION	
					ELECTRICAL AXIS		VENTRICULAR HYPERTROPHY									
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
No. of cases examined:	25		25		25		25		25		15		17		25	
Correct diagnosis	11	44	18	72	11	44	14	56	17	68	12	80	6	36	3	12
Fairly correct diagnosis	5	20	6	24	0	—	2	8	5	20	1	7	7	41	5	20
Erroneous diagnosis	3	12	1	4	0	—	0	—	1	4	1	7	1	6	6	24
Noninformative	6	24	0	—	14	56	9	36	2	8	1	7	3	18	11	44
Value with regard to:																
Correct diagnosis		5		2		5		4		3		1		6		7
Fairly correct diagnosis		3		2		6		4		3		5		1		3
Least erroneous diagnosis		5		2		1		1		2		4		3		6
Greatest utility		5		1		8		6		3		2		4		7
Total points		18		7		20		15		11		12		14		23
Ranking order		6		1		7		5		2		3		4		8

artery, and from puncture of an artery. Oxygen analyses were carried out simultaneously with the apparatus of Chastonay[35] and the Brinkman Hemoreflector, sometimes also controlled by the van Slyke apparatus. Calculations of the pulmonary resistance and the cardiac output were made with the use of the Fick principle.

Circulation time (arm-tongue) was determined by intravenous injection of 2 c.c. of Decholin, before and after oxygen apnea.

Ballistocardiography was performed in the latter one-half of the series by means of a piezo-electric ballistocardiograph, connected to an electrocardiograph, both of Elema's design.[36]

At operation, the surgeon (H. B. W.) in each case tried to estimate the size of the mitral orifice and the degree of regurgitation present before and after the valvulotomy.

Autopsy was performed according to a special scheme.

RESULTS

Preoperative Studies.—Even a superficial look at Table I will disclose the lack of conformity in the diagnoses arrived at by the different methods. It is also obvious that in several instances the result of the examination was noninformative (O). If the surgeon's impression be taken as a verification of the true hemodynamic conditions in the operated cases,* and the diagnosis arrived at by the majority of the methods in the nonoperated cases considered as most probably true, then the distribution of the diagnoses, graded as "correct," "fairly correct," "erroneous," and "noninformative" will be as in Table II (upper part). The scores with regard to these qualities is given in the lower part of Table II. In order of usefulness for the discrimination between preponderant mitral stenosis and mitral regurgitation the methods in our material rank as follows: (1) auscultation, (2) heart roentgenography, (3) angiocardiography and electrokymography, (4) unipolar chest lead electrocardiogram, (5) apex beat, (6) determination of electric axis in the standard electrocardiogram, and (7) pcv tracings at cardiac catheterization. (Fig. 2.)

It should, however, be borne in mind that cases of pure or almost pure mitral stenosis dominate the present material—as they do in any unselected material of mitral valvular defects. The above scoring, therefore, may give a somewhat erroneous impression of the best means of diagnosing mitral regurgitation, if these differ from those of diagnosing mitral stenosis. In the six cases of predominant mitral regurgitation, however, the diagnostic ranking order does not differ much from that of the total material.

Furthermore, the pcv tracings from the cardiac catheterizations were revised, in accordance with our present experience, in order to ascertain whether this would result in a different impression from that of the Tables I and II.

The revision resulted in a re-evaluation of five tracings (Patients M.N., E.B., A.P., R.A., and M.V.N.). Probable influence of propagated pulmonary artery systolic pressures was considered to give a false impression of regurgitation in Patients R.A. and M.V.N. The "I" component was therefore dropped in these cases. The systolic wave was regarded as not exceeding normal in Patient A.P. The tracings of Patients M.N. and E.B. were considered unsuitable for

*In the only case (H. N.) in which the surgeon was not in agreement with the majority of the methods there is strong reason to believe that he was right.

decision for other technical reasons. The low score of cardiac catheterization in differentiating between stenosis and regurgitation is not much influenced by this revision. In our hands, therefore, catheterization has not given as much information as originally hoped for.

We have only had recourse to the ordinary Decholin method of determining circulation time. From our experience with this method and with angiocardiography, however, we believe that more refined methods such as the isotope or dye methods of fractionated determining of the circulation time may yield even more valuable information. Although, as recently stated by Pearce and associates,[22] complex factors influence the circulation time, the shape of the initial portion of the curve may nevertheless be determined by hemodynamic factors related to the mitral orifice, provided aortic valvular defects can be excluded.

CASE REPORTS

The previous section gave a somewhat numerical viewpoint on the matter. It may be of interest to discuss also some illustrative cases.

The material includes two cases of mitral regurgitation, proved at operation (Patients A.Ld. and G.K.) and three cases of clinically probable mitral regurgitation (Patients B.B., E.M., and U.R.). In addition, noteworthy mitral regurgitation (I, SI) was indicated by one or more methods in seven cases of mitral stenosis. In five of these, operations failed to confirm the diagnosis of regurgitation while in one case some regurgitation was found at operation; in the remaining case, no operation was performed. Some regurgitation was found at operation in one patient with no indication of regurgitation at preoperative examinations.

In Patient A.Ld. the apical systolic murmur was short and did not exceed Grade III and there was a typical rumbling diastolic murmur. The apex beat was not palpable. The patient had auricular fibrillation, normal electrical axis, and possibly some slight left ventricular hypertrophy in unipolar precordial leads. The blood pressure was 160/110 mm. Hg. The heart was moderately enlarged (absolute heart volume 1,080 c.c.; per square meter body surface, 630 c.c.), chiefly due to enlargement of the left auricle. There was also some enlargement of the left ventricle, but it was difficult to decide whether this was due to the hypertension. Angiocardiography verified this enlargement of the left ventricle, but otherwise the contrast behaved as in our cases of mitral stenosis. Electrokymography was not performed as the patient had auricular fibrillation. At cardiac catheterization, the pcv tracing showed fairly marked systolic waves. At the time when this patient was operated upon, we were rather sceptical as to the diagnostic significance of systolic pcv waves in auricular fibrillation. Neither the moderate systolic murmur nor the slight enlargement of the left ventricle, in the presence of hypertension, troubled us unduly, as we had seen similar features in other patients who were found to have predominant mitral stenosis. The operative findings, therefore, were a great surprise to us. There was no appreciable stenosis, as the surgeon judged that he could easily pass two fingers through the mitral orifice. The mitral valve was not fibrous or membranous as in the typical cases, but rather like a muscular ring. There was moderate regurgitation through the orifice, but less than might have been expected through this big opening. The surgeon had an impression that in systole the mitral orifice was compressed against the left ventricular wall and thus to some extent occluded. The postoperative course was uneventful. There was no change in the auscultatory findings.

Patient G.K. was operated upon as an explorative procedure, on the patient's own demand. The preoperative examinations had indicated a fair degree of regurgitation in addition to the stenosis.

Physical examination revealed together with the rumbling diastolic murmur at the apex also a systolic murmur Grade IV at the axilla but much less over the apex (Fig. 3, middle row). Blood

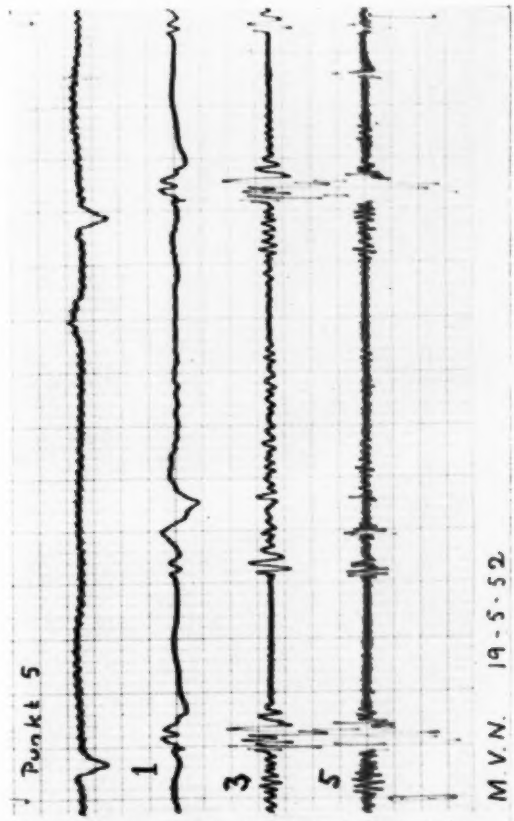


Fig. 3 *A*.—Phonocardiograms from four patients. Preoperative (left) and postoperative (right) phonocardiograms from the apex in a case of pure mitral stenosis with successful operation.

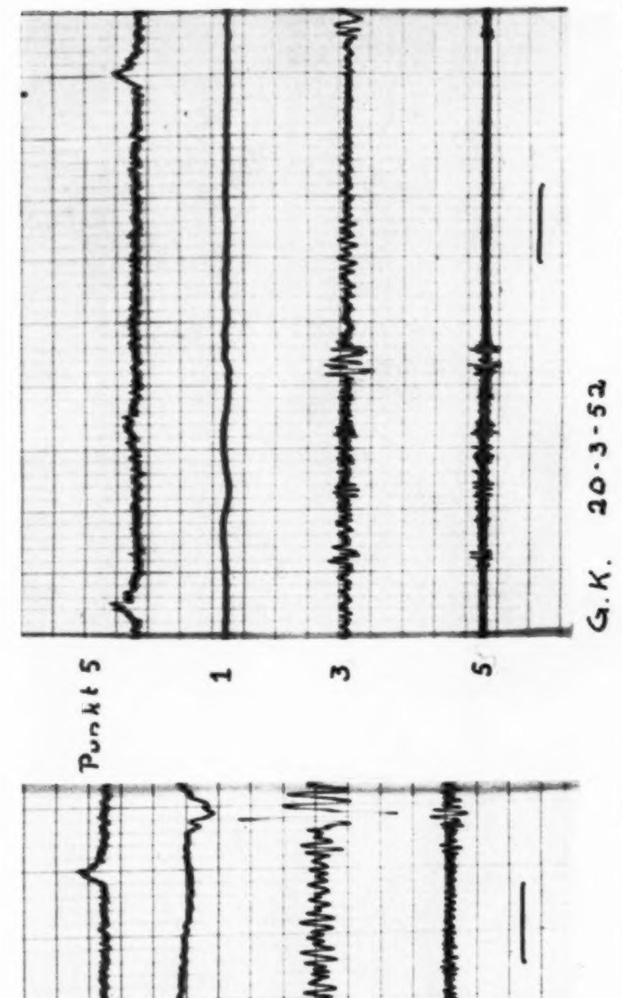


Fig. 3B.—Apex (left) and a few centimeters to the left of the apex (right) phonocardiograms in Patient G. K. who was found at operation to have predominant mitral regurgitation.

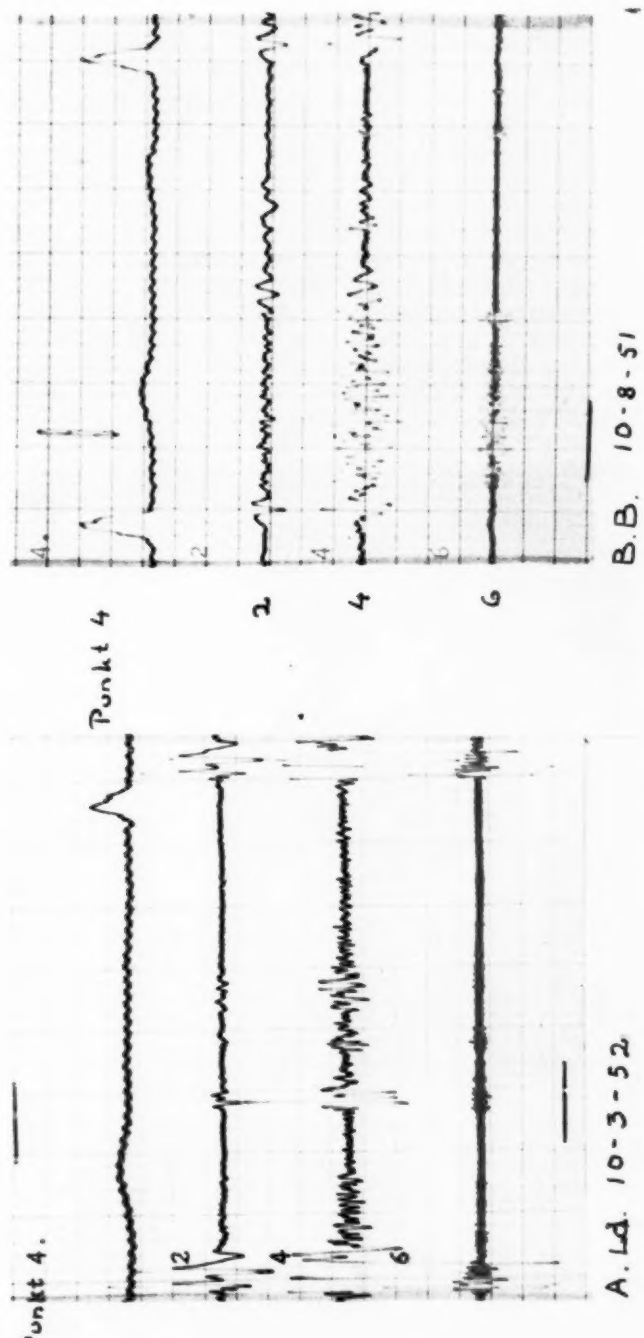
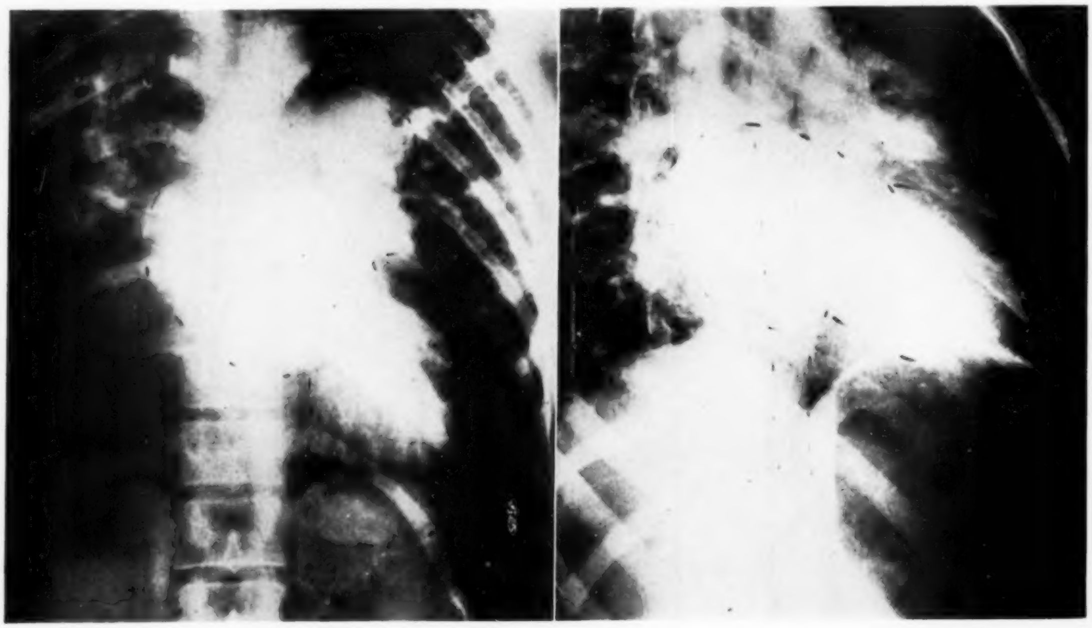


Fig. 3C.—Apex phonocardiograms of Patient A. Ld. (left), who at operation was found to have predominant mitral regurgitation, and of Patient B. B. (right), with the clinical diagnosis of predominant mitral regurgitation.

pressure was 100/60 mm. Hg. The electrocardiogram showed auricular fibrillation, normal electrical axis, no marked ventricular hypertrophy. Roentgenograms and angiocardiograms were considered to indicate predominant mitral stenosis.

At operation, which also revealed an extensive adhesive pericarditis, the mitral valve was found to be partly calcified and deformed into a slit of at least 4 cm. length. Through this orifice there was a strong regurgitant blood jet, and the surgeon felt convinced that the regurgitation was the major hemodynamic defect. Therefore, he only tried to dilate the lateral commissure delicately in an attempt to mobilize the valves better. In this case there has been some postoperative decrease in the intensity of both murmurs.

Patient B.B. may represent a case of almost pure mitral regurgitation, as an early manifestation of a mitral valvulitis, (the later course of which may be the conversion into a scarred mitral stenosis). The main (and only definitely audible) cardiac murmur present was systolic, at the apex of Grade V. She had a forceful apex beat. Blood pressure was 130/70 mm. Hg. Roentgenogram showed relative enlargement of the left ventricle; at angiocardiography (Fig. 4) there was a stagnation of the contrast medium in the left side of the heart, the auricle and the ventricle being well opacified almost simultaneously, giving an impression of blood being shuffled to and fro between these two chambers. Unfortunately, no pcv tracings were obtained at cardiac catheterization. Electrokymography supported the diagnosis of mitral regurgitation.



A. *B.*

Fig. 4.—Angiocardiograms from *A*, Patient M. V. N. with pure mitral stenosis and *B*, Patient B. B. with a diagnosis of predominant mitral regurgitation. Note the small size and lesser opacification of the left ventricle in Patient M. V. N. as compared to the larger size and greater density in Patient B. B.

Two other cases are worthy of mention. Patient A.A. had an enormous heart, estimated to be 2,150 c.c. at roentgenography, corresponding to 1,280 c.c. per square meter body surface. Both the left auricle and the left ventricle were large. There was a Grade IV apical systolic murmur and typical long rumbling diastolic murmur. Blood pressure was 120/90 mm. Hg. The electrocardiogram showed normal electric axis and no marked ventricular hypertrophy. No pcv tracing was obtained in this enormous heart. Despite advice to the contrary, the patient insisted upon operation, which was then performed. There was a calcified mitral orifice, admitting only the

tip of a little finger. Both commissures were fractured by the surgeon's finger, and the final size of the orifice was judged to be one and one-half fingers in diameter. In the postoperative course the patient had severe air hunger and finally he succumbed to this on the third postoperative day in circulatory-respiratory collapse. During these days the systolic murmur was grossly increased to Grade VI, high-pitched, and easily audible without a stethoscope. An intense systolic thrill was also felt at the corresponding site. Autopsy revealed a tear of 8 mm. in the medial commissure and a corresponding but incomplete tear in the lateral commissure. The change in the quality of the systolic murmur must, reasonably, be ascribed to an increase of the regurgitation.

Patient S.O., a 44-year-old woman (who is not included in the material reported in Table I), also applied for valvulotomy but was turned down because of a harsh apical systolic murmur, Grade V, together with the rumbling diastolic murmur of mitral stenosis. The blood pressure was 110/85 mm. Hg. The systolic murmur and a marked enlargement of the left ventricle together with left auricular enlargement were considered evidence of considerable mitral regurgitation. One year later the patient died in cardiac decompensation. Autopsy revealed a mitral orifice permitting more than two fingers, but the valves and chordae tendineae were very thick, fibrotic, and deformed. A diagnosis of mitral regurgitation was made.

This patient had had rheumatic fever at the age of 8 and 12 years. The first diagnosis of a valvular lesion was made at the age of 28. Although it is probable that many a mitral stenosis in its earliest phase passes a stage characterized by a wide orifice with predominant regurgitation, this patient, on the other hand, certainly represents a type of persisting wide open orifice, which, depending upon dynamic relationships, may or may not be accompanied by much regurgitation.

POSTOPERATIVE CHANGES

The dilatation of the mitral orifice by any one of the methods employed will improve the passage of blood from auricle to ventricle, but also involves the risk of a regurgitant blood stream in ventricular systole. Such a regurgitation may be analyzed by the same methods as were used preoperatively. The apex beat, however, is usually of little value, since the heart is felt pulsating behind the soft parts at the place of the resected rib. Likewise, it is our experience that there is a general tendency to a leftward axis shift of the electrocardiogram after operation, probably due to a somewhat altered anatomic position of the heart secondary to postoperative changes of the left pleura and the diaphragm. Some left axis shift was almost regularly observed, regardless of whether the operation was successful or not. Of major importance are changes in auscultatory findings, roentgenogram (enlargement of left ventricle), and typical curves obtained at electrokymography and cardiac catheterization (pcv tracings). Angiocardiograms were not performed postoperatively.

The result of a comparison between pre- and postoperative findings in fourteen cases are reported in Table III and summarized in Table IV.

It is obvious from the cases analyzed in these tables that there is no apparent increase of the systolic murmurs, while a decrease of the diastolic murmur is a common finding. The electrical axis is not changed or shifted to the left. The right ventricular hypertrophy in the electrocardiogram is either unaltered or decreased. Partly due to the resection of the left auricular appendage, and also, in many cases, to improved hemodynamic conditions, the left auricle has decreased in size, whereas in some cases there is an increase in left ventricular size. In two cases this is paralleled by increased systolic pcv waves. Electrokymography is much more difficult after the resection of the auricular appendage, as the best recording points have sometimes been lost. There appears, however, to be a decrease in the degree of stenosis and an increase in regurgitation in the majority

TABLE III.

PATIENTS	OPERATION			APICAL MURMURS				ELECTROCARDIOGRAPHY			
	VALVULAR SIZE		THERAPEUTIC RESULT	SYSTOLIC		DIASTOLIC		ELECTRICAL AXIS		VENTRICULAR HYPERTROPHY	
	B	A		B	A	B	A	B	A	B	A
S. N.	<1 finger	1½ to 2 fingers	Excellent	Gr. III	Gr. I	Loud	Reduced	R	R	R	Slightly reduced
R. H.	Little finger	1½ fingers	Very good	Faint	Faint	Moderate	Reduced	R	Almost normal	R	Reduced
S. K.	Fountain pen	>1 finger	Very good	Gr. II	Gr. II	Moderate	Same	R	N	R	(r)
E. A.	Tip of little finger	1½ fingers	Good	Gr. II	Gr. II	Moderate	Same	R	N	r	r
E. B.	Pen	2 fingers	Very good	Faint	Faint	Moderate	Reduced	R	N	(r)	(r)
M. N.	Pea	2 fingers	Good	Faint	Faint	Moderate	Same	R	N	r?	r?
V. L.	Pen	>1½ fingers	Very good	Faint	Faint	Moderate	Reduced	N	N	(r)	(r)
E. R.	Tip of little finger	2 fingers	Very good	Faint	Faint	Weak	Same	N	N	RL	rL
A. P.	Index finger	2 fingers	Very good	Faint	Faint	Moderate	Reduced	N	N	r	(r)
M. Ö.	Pencil	1½ fingers	Good	Faint	Faint	Moderate	Reduced	N	L	R	R
S. H.	Pencil	1½ fingers	Very good	Gr. III	Gr. II	Moderate	Reduced	R	N	None	Same
R. A.	Tip of little finger	>1 finger	Very good	Faint	Faint	Moderate	Same	R	L	None	Same
A. Ld.	2 fingers	2 fingers	No change	Gr. III	Gr. III	Moderate	Same	N	N/L	L	L
M. V. N.	Pencil	1½ fingers	Very good	Faint	Faint	Loud	Reduced	R	R	R	R

TABLE III (CONTINUED)

PATIENTS	ROENTGENOGRAPHY				ELECTROKYMOGRAPHY				CATHETERIZATION (PCV)			
	LEFT AURICLE		LEFT VENTRICLE		STENOSIS		INSUFFICIENCY		PRESYSTOLIC WAVE		SYSTOLIC WAVE	
	B	A	B	A	B	A	B	A	B	A	B	A
S. N.	Large	Reduced	Normal	Same	—	None	—	Marked	—	—	—	—
R. H.	Large	Reduced	Normal	Same	—	None	—	Slight	—	—	—	—
S. K.	Large	Reduced	Normal	Increased	—	None	—	Some	Tall (F) None	Same (F) None	Small Broad	Increased Tall
E. A.	Large	Reduced	Moderately enlarged	Same	—	—	—	—				
E. B.	Large	Reduced	Slightly enlarged	Same	Some	None	None	Some	Not comparable: Preoperative tracings unreliable			
M. N.	Large	Reduced	Large	Same	—	—	—	(Doubtful)	(F) None	(F) None	Moderate	Same
V. L.	Large	Reduced	Normal	Same	—	—	—	—	Tall	Reduced	Small	Increased
E. R.	Large	Reduced	Normal	Slightly increased	Some	Same	Some	Same	Marked	Increased	Marked	Increased
A. P.	Large	Reduced	Somewhat enlarged	Same	Marked	None	None	Marked	Marked	Increased	None	Increased
M. Ö.	Large	Reduced	Somewhat enlarged	Same	Some	—	Slight	—	Tall	Same	Moderate	Same
S. H.	Large	Same	Normal	Same	Some?	None	Some	Same	—	—	—	—
R. A.	Large	Reduced	Slightly enlarged	Same	Some	None	Slight	Some	Tall	—	Tall	—
A. Ld.	Large	Same	Slightly enlarged	Same	—	—	—	—	(F) None	—	Tall	—
M. V. N.	Large	Reduced	Normal	Increased	Some	None	Slight	Some	(None)	Moderate	Tall (= Pulm. art.)	Moderate

B = before operation
A = after operation
F = auricular fibrillation

N = normal
L = left
R = right

l = left; less well-marked features
r = right; less well-marked features

of the acceptable tracings. There is no conclusive parallel between these observations and those from roentgenogram or catherization. In most of the clinically successful cases the pressure recordings at cardiac catheterization show a reduction of pressures in the pulmonary circulation. There is less constancy in the appearance of the pcv tracings, but in four cases there was a clear increase in the amplitude of the systolic waves.

What is the significance of these findings? Apparently, the lack of conformity between the results of various diagnostic methods, apparent already in the preoperative studies, is equally common in this group of observations. It is interesting that changes indicating increased regurgitation at electrokymography and catherization are not paralleled by notable changes in the quality of the systolic murmur. It must be admitted, though, that auscultation, even when supported by phonocardiography, is less amenable to comparisons than objective recordings. A moderate increase in left ventricular size at roentgenography after valvulotomy may probably not be taken per se as indicating mitral regurgitation and may thus not be taken to support any one of the other results.

TABLE IV. SUMMARY OF OBSERVED CHANGES AFTER VALVULOTOMY IN FOURTEEN CASES

	INCREASE	NO CHANGE	DECREASE	REMARKS
Auscultation				
Apical systolic murmur	0	12	2	
Apical diastolic murmur	0	6	8	
Electrocardiography				
Right axis deviation	0	5	9	
Right ventricular hypertrophy	0	9	5	
Roentgenography				
Left auricular size	0	2	12	
Left ventricular size	3	11	0	
Electrokymography				Complete studies in only six cases
Stenosis curve		1	5	
Regurgitation curve	4	2		
Catheterization (pcv)				Complete studies in only nine cases
Presystolic wave	2	2	1	
Systolic wave	4	2	1	
Pressures in pulmonary circulation	2	3	7	Studied in twelve cases

DISCUSSION

This study was started in an attempt to investigate which diagnostic methods gave the most valuable information as to the degree of mitral regurgitation in mitral stenosis. Some of these methods are old and known to every physician; they cost nothing and do no harm to the patient.[23] Others are quite modern, require expensive outfits and specialist training and may—rarely but unpredictably—be harmful and, in single instances, even lethal. When comparing the diagnostic values of these methods, several factors must be taken into con-

sideration, for example, reliability of positive results, percentage of noninformative results, and hazards as well as technical and economic factors in the use of the different apparatus.

Murmurs.—Quite recently, Spiegl and associates[24] have reported changes in auscultatory findings after mitral valvuloplasty in eighteen patients. They found reduction of the diastolic murmur in all their patients and in one-half of them an increase in the systolic murmur. They consider the reduction in the diastolic murmur to be the best clinical index to indicate postoperative improvement. Our experience is, on the whole, in agreement with these findings. It must, however, be remembered that pleuropericardial alterations secondary to the operation may contribute to the reduction of the audibility of any murmur.

As pointed out earlier in this paper, the evaluation of the murmurs in mitral valvular disease is one of the most difficult and controversial in cardiology. At the present point of our investigation we are inclined to adhere to the following viewpoints:

There is one group of apical systolic murmurs, approximately of Grades II to III, which may or may not mean mitral regurgitation. Only additional examinations of the type described in this paper will tell whether there is mitral regurgitation or not. Patients, in whom systole is clear, or only a very faint (Grade I) systolic murmur is heard in preoperative studies, will not show any noteworthy mitral regurgitation. It is not clear yet if this also applies to the postoperative state. It may be that mitral regurgitation due to commissurotomy is not equivalent to regurgitation of more natural origin.

Loud, harsh systolic murmurs without noteworthy diastolic murmurs in the early stages of a chronic rheumatic carditis may represent mitral regurgitation. In some patients with proved mitral regurgitation there has been a very loud and harsh apical systolic murmur with a very intense thrill. If other explanations (ventricular septal defects, aortic stenosis) be excluded, this murmur may reasonably be regarded as indicative of mitral regurgitation.

Electrocardiogram.—The axis deviation seemed to be of minor diagnostic significance in our preoperative studies. Recent studies by Rasmussen and Böe[25] and by Nylin[26] have shown that a normal electric axis is found in the majority of their cases of mitral stenosis. Even single instances of left axis deviation were noted by them, but may have been due to overlooked factors. It seems justified to state, however, that right axis deviation indicates predominant mitral stenosis, while left axis deviation indicates some complicating factor and normal electric axis is of no significance. A general tendency to leftward axis shift was observed after operation without correlation to the degree of clinical improvement. Unipolar chest leads, in our material, were more useful than in that of Rasmussen and Böe.[25]

Roentgenography, Angiocardiography, and Electrokymography.—In the preoperative scoring table, roentgenography ranked second, after auscultation, with angiocardiography and electrokymography next. As for ordinary roentgenography, the shape of the left auricle is usually easy to ascertain, whereas the delimitation of the left ventricle is sometimes difficult. In this respect, as well as for the study of cardiac hemodynamics, angiocardiography was found to be very useful. In 1944 Grishman and associates[27] reported on angiocardiography in mitral valvular disease. Probably due to the fact that their apparatus did not

permit enough serial exposures in a short time, their interest was focused more upon configuration than upon hemodynamics. With modern equipment the latter factor is perhaps more interesting and we believe firmly in the value of angiocardiography in all problematic cases of mitral valvular disease. Parkinson,[28] in a survey of the radiologic diagnosis of rheumatic heart disease, seems rather sceptical as to the diagnostic significance of the configuration of the heart at ordinary chest roentgenography, but believes in the potential value of kymographic representations of the left auricular systolic pulsations in mitral regurgitation. However, electrokymography is a delicate procedure, and particularly in

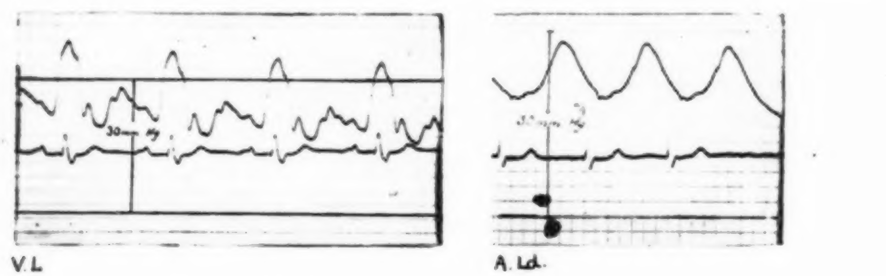


Fig. 5.—Pcv pressure tracings from six of the patients. The curve from Patient V. L. was considered typical of pure mitral stenosis with little or no regurgitation. The curve from Patient A. Ld. shows the "tent"-shape we believe typical of predominant mitral regurgitation. Patient R. A. was considered as displaying signs of stenosis and regurgitation. No regurgitation was, however, found at operation and the systolic waves in this patient, as well as in Patient M. V. N., who also had a pure stenosis, may be ascribed to pulmonary artery pressure going through (despite 98 per cent arterial saturation in samples drawn). The tracings from Patient M. N., who had a pure stenosis at operation, are presented as typical of some curves obtained in fibrillating patients. In Patient E. M., finally a presystolic wave is seen. This patient, however, clinically appeared as a case of predominant regurgitation.

auricular fibrillation good tracings are rarely obtained. Under favorable circumstances, electrokymography is very illuminating, but its usefulness is limited in many patients. Furthermore, the interpretation of the curves still seems to be a subject of discussion.[21] Despite our previous reservations as to the determination of left ventricular size in ordinary chest films, the result of our evaluation appears fairly satisfactory in comparison with the other methods. The information derived from the sagittal view of the heart perhaps contributed most to our decisions in doubtful cases. (Fig. 6.)

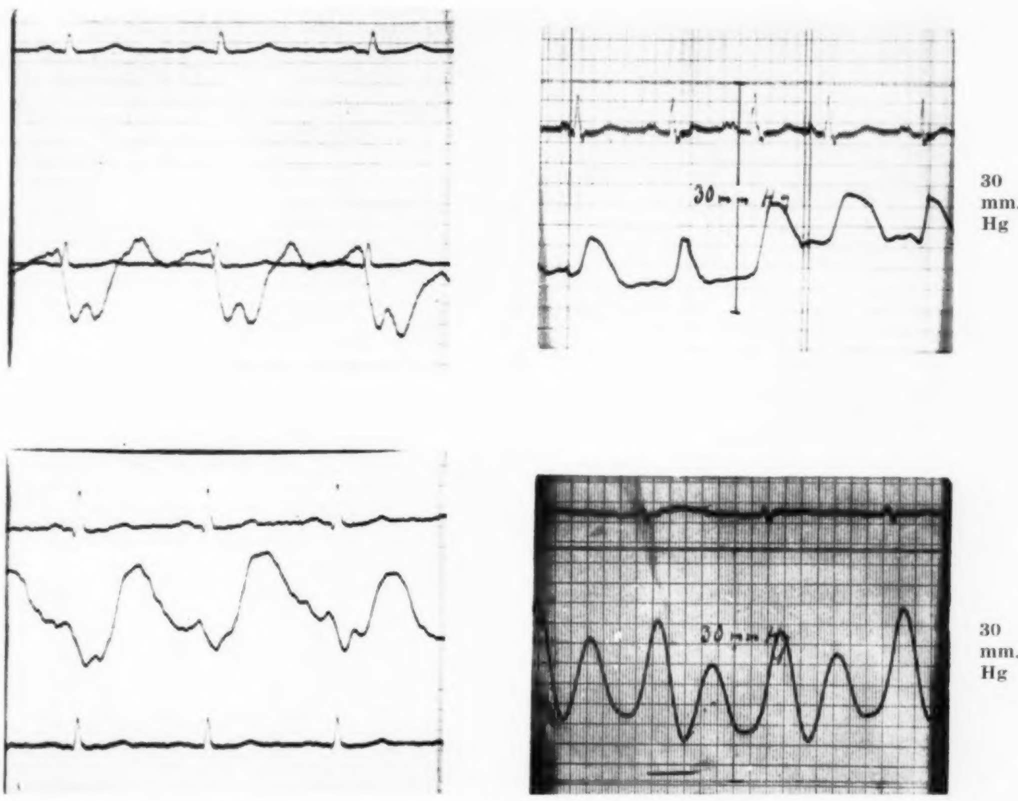


Fig. 6.—Electrokymograms (left) and pcv tracings (right) from Patient A. P., before operation (upper row) and after (lower row). The preoperative curves indicate almost pure stenosis. The postoperative electrokymogram was considered typical of regurgitation, and a marked systolic wave has also appeared in the pcv curve.

Cardiac Catheterization.—One of the most disturbing and controversial matters is the interpretation and evaluation of the systolic pressure waves in pulmonary capillary venous (pcv) tracings. Here, the opinions of the workers show marked differences.

Lagerlöf and Werkö[29] declared that an unusually early and high systolic pressure rise was indicative of mitral regurgitation. A later study from the same laboratory (Eliasch[30]) concluded that the existence of mitral incompetence could not be assessed with certainty from the form of the pcv pressure pulse. Dexter

and associates,[31] on the contrary, stated that the presence of mitral insufficiency might be detected accurately from the contour of the pulmonary capillary pressure tracings and they even estimated quantitatively the degree of regurgitation. Draper and associates[32] abstained from any statements on this matter. Husfelt and Warburg[33] have recently advanced the theory that pcv tracings in regurgitation lack what they call "systolic collapse" in the early phase of systole. We have re-examined our tracings from this point of view and found that most, but not all, of our systolic pressure waves considered as indicating some degree of regurgitation behaved as stated by these authors. Still, to our mind, the very typical regurgitation curves are tall, "tent-shaped" systolic waves. (Fig. 5, Patient A.Ld.)

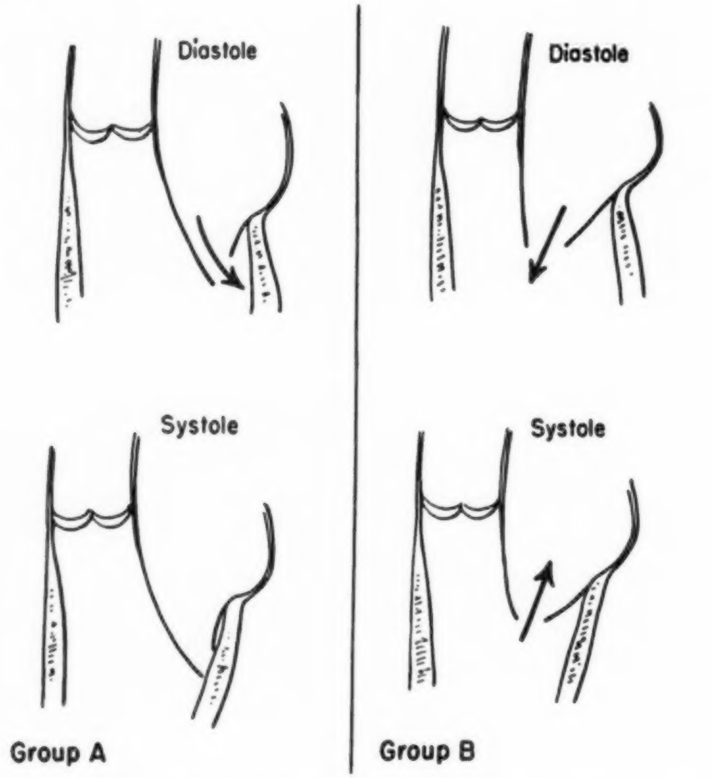


Fig. 7.—This figure demonstrates the effects of different anatomic types of mitral valvular lesions, depending upon the orientation of the orifice. (From Harken, Ellis, Dexter, Farrand, and Dickson: Circulation 5:349, 1952.)

So far, our experiences with pcv tracings have been less favorable than originally expected. This may partly be a question of individual technique but the fact that we are in agreement with Eliasch on this point makes us believe that good pcv tracings are not always obtainable. It is possible that recording on a direct-writing electrocardiographic machine offers distinct advantages in that the catheter can be pushed back and forth until ideal tracings are recorded. However, this statement has bearing only upon one detail. The quantitative determination of pressures, naturally, retains its great importance.

In most centers where mitral stenosis is subject to surgical treatment besides the usual clinical, electrocardiographic, and radiologic examination of the patients, cardiac catheterization is available. Electrokymography and, in particular, angiocardiography seem to be less used. At present, our impression of the usefulness of the latter methods for the problems discussed in this paper is a favorable one. In view of the expert knowledge necessary, and the expensive equipment required, their use may still be considered as somewhat experimental and we do not yet recommend them for routine use, except in large centers of thoracic surgery, where these methods can be used for a wide range of diagnostic examinations, concerning the heart and large vessels as well as the lungs.

CONCLUSIONS

This paper contains some data on the problem of the diagnosis of mitral valvular disease. Whether it contributes anything to a more precise knowledge of the subject or rather creates further confusion is for the reader to decide. In the authors' opinion, it provides some "Ehrenrettung" not only to the diagnosis of mitral regurgitation but also to physical examination and radiology in the discrimination between stenosis and regurgitation. The starting point in our study was the surgeon's requirement of an exact diagnosis. The first and, so far, only case where a major diagnostic error was made has, furthermore, introduced the problem of whether the degree of regurgitation and the size of the mitral orifice are two different things or not. From our present knowledge of valvular mechanics and intracardiac hemodynamics it would appear as if the direction of the valvular opening during systole must play a definite role for the degree of regurgitation, as already indicated by Harken and associates[3] (Fig. 7).

It would be of value, therefore, to find reliable methods for the estimation of the size of an orifice that may be larger than judged from the degree of regurgitation.

SUMMARY

In order to investigate which diagnostic signs were most useful for the evaluation of the degree of mitral regurgitation in cases of mitral valvular disease, several methods were employed in a number of candidates for mitral valvulotomy. These methods were: palpation of the apex beat, auscultation, standard and unipolar electrocardiography, electrokymography, roentgenography of the heart, angiocardiography, and cardiac catheterization. In addition, ballistocardiograms were recorded in some patients and determinations of circulation time with Decholin were made.

The individual methods were put to a scoring test, the results of which are tabulated and discussed.

Since auscultation of cardiac murmurs was found to be most informative, a more detailed stating of the often rather vague diagnostic criteria given in the literature has been advanced for the purpose of further discussion.

The possibility that the size of the mitral orifice and the degree of regurgitation may not always parallel each other has been discussed and the need for a differentiation here has been stressed.

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REFERENCES

1. Glover, R. P., Bailey, C. P., and O'Neill, T. J. E.: Surgery of Stenotic Valvular Disease of the Heart, J. A. M. A. **144**:1040-1057, 1950.

2a. Baker, C., Brock, R. C., and Campbell, M.: Valvulotomy for Mitral Stenosis. Report of Six Successful Cases, Brit. M. J. **1**:1283, 1950

2b. Baker, C., Brock, R. C., Campbell, M., and Wood, P.: Valvulotomy for Mitral Stenosis, Brit. M. J. **1**:1043-1055, 1952.

3. Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E., and Dickson, J. F.: The Surgery of Mitral Stenosis. III. Finger-fracture Valvuloplasty, Ann. Surg. **134**:722-742, 1951.

4. Crafoord, C., Bergulund, F., Eliasch, H., and Werkö, L.: Kirurgisk behandling av mitralisstenos, Nord. Med. **45**:831-835, 1951.

5. Bland, E. F.: Surgery for Mitral Stenosis. A Review of Progress, Circulation **5**:290-299, 1952.

6. Harken, D. E., Ellis, L. B., Dexter, L., Farrand, R. E., and Dickson, J. F.: The Responsibility of the Physician in the Selection of Patients With Mitral Stenosis for Surgical Treatment, Circulation **5**:349-362, 1952.

7. Werkö, L.: Kirurgisk behandling av hjärtsjukdomar. III. Mitralisfel, Nord. Med. **47**:391-393, 1952.

8. Wulff, H. B., Biörck, G., Bergh, N. P., Krook, H., Axén, O., and Lundskog, O.: Studies in Mitral Stenosis. I. Results of One Year's Surgical Treatment of Mitral Stenosis, Acta med. Scandinav. In print.

9. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York, 1945, New York Heart Association.

10. Lewis, T.: Diseases of the Heart, London, 1937, The Macmillan Company.

11. White, P. D.: Heart Disease, New York, 1951, The Macmillan Company.

12. Levine, S. A.: Clinical Auscultation of the Heart, Philadelphia, 1949, W. B. Saunders Company.

13. Bramwell, C., and King, J. T.: The Principles and Practice of Cardiology, New York and London, 1942, Oxford University Press.

14. Lutembacher, R.: Le rétrécissement mitral, Paris, 1950, Masson & Cie.

15. Svartz, N., and Ernberg, T.: Prognosen vid olika typer av reumatiska valvelfel, Nord. Med. **33**:757-759, 1947.

16. Liljestrand, G., Lysholm, E., Nylin, G., and Zachrisson, C. G.: The Normal Heart Volume in Man, AM. HEART J. **17**:406-415, 1939.

17. Jonsell, S.: A Method for the Determination of the Heart Size by Teleroentgenography (A Heart Volume Index), Acta radiol. **20**:325-340, 1939.

18. Axén, O., and Lind, J.: Electrocardiographic Recording in Angiocardiography With Synchronous Serial Photography at Right-angled Planes, Cardiologia **16**:60, 1950.

19. Axén, O.: Angiocardiografi, Medicinska framsteg **2**:175-182, 1952.

20. Engström, B., Kjellberg, S. R., Persson, L., and Rudhe, U.: Some Aspects of the Use of Electrokymography in Cardiac Investigations, Acta radiol. **31**:435, 1949.

21. Dack, S., and Paley, D. H.: Elzctrokymography. II. The Great Vessels and Auricular Electrokymograms, Am. J. Med. **12**:447-471, 1952.

22. Pearce, M. L., Lewis, A. E., and Kaplan, M. R.: The Factors Influencing the Circulation Time, Circulation **5**:583-588, 1952.

23. Biörck, G., Axén, O., Krook, H., Andrén, L., and Wulff, H. B.: Diagnosen mitralisinsufficiens, Nord. Med. In print.

24. Spiegl, R. J., Long, J. B., and Dexter, L.: Clinical Observations in Patients Undergoing Finger Fracture Mitral Valvuloplasty. I. Ausculatory Changes, Am. J. Med **12**:626-630, 1952.

25. Rasmussen, H., and Böe, J.: The Natural History of the Electrocardiogram in Mitral Stenosis, Cardiologia **18**:33-44, 1951.

26. Nylin, G.: Isolated Mitral Stenosis, Acta med. Scandinav. **142**:797-815, 1952.

27. Grishman, A., Sussman, M. L., and Steinberg, M. F.: Angiocardiographic Analysis of the Cardiac Configuration in Rheumatic Mitral Disease, Am. J. Roentgenol. **51**:33-43, 1944.

28. Parkinson, J.: The Radiology of Rheumatic Heart Disease, Lancet **1**:895, 1949.

29. Lagerlöf, H., and Werkö, L.: Studies on the Circulation in Man. VI. The Pulmonary Capillary Venous Pressure Pulse in Man. Scandinav. J. Clin. & Lab. Invest. **1**:147-161, 1949.

30. Eliasch, H.: The Pulmonary Circulation at Rest and on Effort in Mitral Stenosis, Acta med. Scandinav., Suppl., 1952.

31. Dexter, L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Harken, D. E.: Physiologic Evaluation of Patients With Mitral Stenosis Before and After Mitral Valvuloplasty, Transactions of American Clinical and Climatological Association **62**:1, 1950.

32. Draper, A., Heimbecker, R., Daley, R., Carroll, D., Mudd, G., Wells, R., Falholt, W., Andrus, E. C., and Bing, R. J.: Physiologic Studies in Mitral Valvular Disease, Circulation **3**:531-542, 1951.

33. Husfeldt, E., and Warburg, E.: Problemer vedrörende diagnose og operation af mitralisstenose, Medicinske Fremskridt **2**:156-174, 1952.

34. Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of Circulatory Dynamics at Rest in Mitral Valvular Regurgitation With and Without Stenosis, AM. HEART J. **43**:357, 1952.

35. de Chastonay, J. L.: De la capacité en aéygene du sang et de sa measure. Thèse, Zürich, 1950, S. Karger, Verlag.

36. Biörck, G., and Thorson, A.: Ballistocardiography in Clinical Practice, Cardiologia, supp. 1952. In print.

STUDIES OF FREQUENCY RESPONSE IN BALLISTOCARDIOGRAPHY

J. E. SMITH, M.D.* AND SAMUEL BRYAN, M.A.**

WASHINGTON, D. C.

THE USE of ballistocardiographic devices as diagnostic aids in heart disease has raised the question of interchangeability and comparability of information derived from diverse techniques and approaches to the problem. Most of the early work has been done using ballistic tables of the Starr and Schroeder type[1] (high frequency) and of the Nickerson type[2] (low frequency).

Ballistic measurements directly from the body have been developed by Dock and associates[3] using a photoelectric cell and a coil-magnet-condenser arrangement. Others have used crystal pickups and strain gauges. The photocell, strain gauges, and most crystal pickups are displacement measuring devices. The coil and magnet is a velocity measuring device.

Recently, several types of ballistocardiographs have been made and sold commercially with no attempt at standardization of instrumentation, techniques, and frequency response characteristics. If this type of situation continues, the development of ballistocardiography as a clinical entity will be chaotic as there will be no basis of comparison of tracings. The application of sound engineering principles has been neglected too long.

The phenomena of displacement of the human body in response to the ejection and flow of blood must be examined in the same fashion as an engineer examines the vibratory characteristics of an internal combustion engine, loudspeakers, earthquakes, or other vibratory phenomena. The so-called ballistic effect resulting from the heart beat is a vibration which may be analyzed in terms of frequency, amplitude, time lag, effects of resonance, etc. In order to examine the tracings intelligently, we should know the following: (1) the amplitude-frequency response of the transducer (pickup); (2) the amplitude-frequency characteristics of the insertion network, amplifier, filter or other modifying device; (3) the amplitude-frequency response of the recorder or "tracing machine"; (4) the physiologically significant frequencies of body motion originating in the heart pulsations, and (5) the inherent frequency of the body motion in relation to the frequency of cardiac ejection and blood flow (forcing function).

The first three of these amplitude-frequency response characteristics are inherent in the design and techniques of utilization of the instrumentation and must be patterned to fit the requirements dictated by the physiologically sig-

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*Chief, Medical Standards Branch Medical Div., Off. of Aviation Safety Civil Aeronautics Administration, Washington 25, D. C.

**Electronics Division, National Production Authority, Washington 25, D. C.

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nificant frequencies resulting from and associated with the ejection and flow of blood from the heart.

The two chief requirements to be satisfied by a pickup or transducer are: (1) At any frequency in the operating range the movement of the pickup must produce an electrical signal proportional to the movement. The proportionality factor between the pickup signal and the varying motion must be constant over the expected operating range. (2) The time delay between the motion and the pickup signal must remain constant over the frequency range.

In order to conform with good instrumentation and engineering practices, the amplitude-frequency response of the instrumentation (including the recorder) should be constant throughout the range of frequencies determined to be significant. We propose that deviations from this constant response of more than 0.5 decibel (approximately 6 per cent) shall not be acceptable as fulfilling the required flatness of response criteria.

A recording or tracing will in general consist of information derived from the phenomenon under study and from extraneous sources such as hum (60 and 120 cycles alternating current), random signals inherently generated by the equipment itself, signals generated by body motions not related to the ejection and flow of blood (respiration and body tremor components), and extraneous signals originating in building vibrations and movement of personnel adjacent to the recording apparatus. Spurious signals of this character can in large part be eliminated by limiting the frequency response of the instrumentation. This effectively attenuates signals of frequencies outside of the range of frequencies under study. However, in some abnormalities of the circulation, the high-frequency components of the ballistocardiogram indicate significant motions in the ranges of higher frequency ambients such as body tremor. It is probable that adequate information from ballistocardiograph techniques will demand more than one frequency response characteristic for clinical use.

Circuits which are frequency discriminating are known as filters. A low-pass filter is one that allows low frequencies to go through but attenuates high frequencies. A high-pass filter is the converse of a low-pass filter, and a band-pass filter is one that attenuates above a selected frequency and also attenuates below another selected frequency. Since the most objectionable spurious frequencies occur in the higher range (body tremor and A.C. hum), we shall treat the considerations of low-pass filter criteria later in this paper. When the frequency response is attenuated by a filter to 3 decibels (about 70 per cent) of its maximum value, we label the frequency at this point the cut-off frequency.

The coil and magnet direct-body pickup which was introduced by Dock and Taubman[3] is by the nature of the instrumentation a velocity pickup. Either the coil or the magnet may be attached to the body, and the other is supported by a clamp fastened to a mechanical ground (rigid table, floor, or wall). This pickup generates an electric voltage only when one moves in relation to the other. The voltage generated is proportional to the velocity of the motion, while a static deflection gives zero voltage. High-frequency motions even of low amplitude will therefore yield appreciable signals when compared with a displacement type pickup. Body tremors are most generally encountered above 10 cycles per second

and, when permitted to reach the recorder, tend to obscure the outline of the tracing due to body motions originating from the ejection of blood from the heart. Therefore, the signal is passed through a suitable low-pass filter network to attenuate these tremor components. It should be noted that the design of the filters must be such that there is no distortion of frequency response in the significant pass-band. Filters that cause "rolloffs" in the region of body motions will result in a recording that is an intermediate tracing between velocity and displacement characteristics.

CONVERSION OF VELOCITY SIGNALS TO DISPLACEMENT AND ACCELERATION

In our research we found it desirable to compare velocity with displacement and acceleration ballistocardiograms. Since the coil and magnet is inherently a velocity device, we passed the velocity signal through integrating and differentiating networks to derive our displacement and acceleration recordings, respectively.

An integrating network is one which causes a loss of 6 decibels per octave with increasing frequency when a constant amplitude signal is fed into the network. This means that a given input voltage at 6 cycles per second will yield an output voltage of exactly one-half the magnitude that would be yielded by the same voltage input signal at 3 cycles. This type of network will convert a velocity signal to a displacement signal.

A differentiating network is one that yields a loss of 6 decibels per octave with decreasing frequency when a constant amplitude signal is fed into the network. For a given input voltage the network should yield double the voltage output at 6 cycles per second that would be obtained at 3 cycles per second. This type of network will convert a velocity signal to an acceleration signal.

Fig. 1 illustrates the relationship of the frequency-amplitude characteristics of displacement, velocity, and acceleration curves. These three curves are superimposed so that the point of intersection occurs at 5 cycles (which is arbitrarily selected as the average fundamental frequency of body motion).

It should be noted that the acceleration curve accentuates the higher frequency components and minimizes low-frequency components of the body-motion complex. The displacement curve conversely accentuates the low-frequency components and minimizes the high-frequency signals.

The standards of wave ratios in forty normal adults, when studied as displacement, velocity, and acceleration, are much closer percentagewise when measured as velocity. The displacement H wave is usually more prominent and variable than the velocity H, but the displacement K wave is much more variable and can occur slightly above the base line or deeply below the base line.

The acceleration H wave in normal individuals is sometimes of lower amplitude when compared to displacement and velocity and is composed of two distinct components in many people. The acceleration K wave is always deeply below the base line in normal adults. Higher frequency abnormalities in the ballistic wave show much greater amplitude on the acceleration component.

It is probable that the scatter of body frequencies will affect the displacement and acceleration curves to a greater extent as shown on the frequency re-

sponse curve of Fig. 1. Also, the H wave complex is of a lower frequency than the IJK complex and thus becomes of lower amplitude on the acceleration curve in some people.

Using the electronic micrometer[4] the displacement of the body due to respiration is roughly about 0.002 inch during quiet respiration. The actual displacement due to motion of the diaphragm is influenced by body structure. Tall, thin adults show a body displacement greater than short, thickset individuals due to breathing. In some tall, thin individuals the body displacement due to respiration was as much as 0.005 inch, and in those people it was nearly impossible to obtain accurate displacement ballistocardiograms even with respiration suspended.

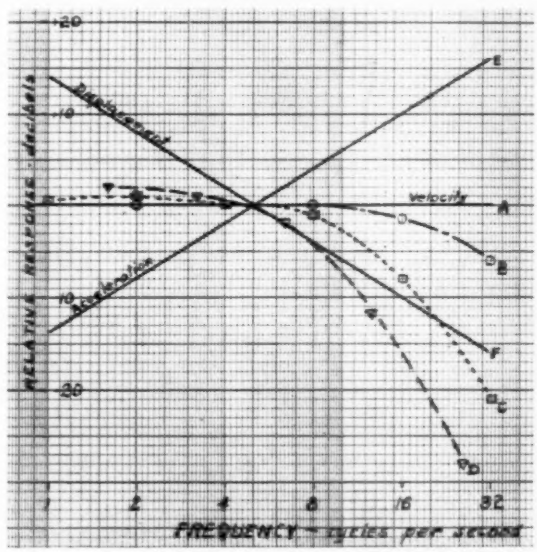

Fig. 1.—Frequency response curves showing relative frequency response of displacement, velocity, acceleration, and filters as related to body motions.

Since the displacement of the body due to ejection of blood is about 0.004 inch in young normal adults, the respiratory interference can easily be appreciated. However, the motion of the diaphragm has little influence per se on the velocity base line. The comparison of displacement velocity wave ratios is demonstrated in Fig. 3.

It is probable that the diaphragm per se exerts little influence on the acceleration curves. For this reason, the effect of ejection and flow of blood during quiet respiration can be much better studied as velocity and acceleration. Some instruments have used the technique of measuring displacement above 2 to 3 cycles and filters to take out motions of the diaphragm (low-frequency filters). This is undesirable because of distortion in the frequency response and resultant changes in wave ratio measurements. Low-frequency filters with a sharp drop tend to advance timing and obliterate the H-wave component.

CASE REPORTS

CASE 1.—A normal 29-year-old pilot. There was no evidence of cardiovascular disease. The displacement, velocity, and acceleration ballistocardiograms are illustrated in Fig. 2. The phase shift and timing show that the acceleration curve is 90 degrees ahead of velocity and velocity is 90 degrees ahead of displacement. There are no visible higher frequency components.

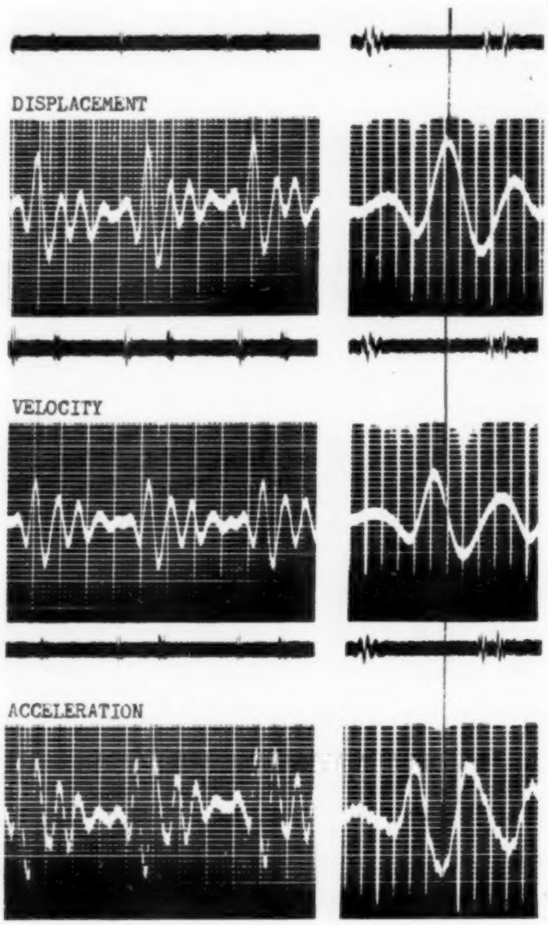

Fig. 2.—Normal 29-year-old pilot. The displacement, velocity, and acceleration curves show phase shift with acceleration ahead of displacement by 180 degrees and ahead of velocity by 90 degrees. There are no visible higher frequency components in these tracings.

CASE 2.—A normal 31-year-old pilot. The velocity and displacement ballistocardiograms are recorded simultaneously so that motions can be recorded from the same heart beat. Respiration was suspended. Note the marked variation in the J-K segment on the displacement curve. The wave ratios of the velocity curve remain constant. The displacement curve was recorded on a photocell. Velocity was recorded on frequency response curve *C* of Fig. 1. The above changes are illustrated in Fig. 3.

CASE 3.—A 47-year-old hypertensive woman. Blood pressure was 240/130. Electrocardiogram showed typical left ventricular strain pattern. This patient had several bouts of paroxysmal auricular fibrillation which lasted only a few hours, and normal sinus rhythm could be restored by

rest alone. The ballistocardiograms are illustrated in Fig. 4. *A*, *B*, *C*, and *D* are tracings taken of frequency response curves *A*, *B*, *C*, and *D* of Fig. 1. The ballistic curves show a short H-I segment and deep J-K segment. The timing is fast. First sound to K = 0.24 second, J = 0.17 second, I = 0.11 second, and H = 0.08 second. As filter action is increased, the H-I segment is obliterated. The H-I segment can still be seen on frequency response *B*. Some cases have been reported in the literature which show the H wave preceding the first sound or peak of the R wave. It is probable that this is not true and the reason is probably due to low-frequency response of the transducer-filter network.

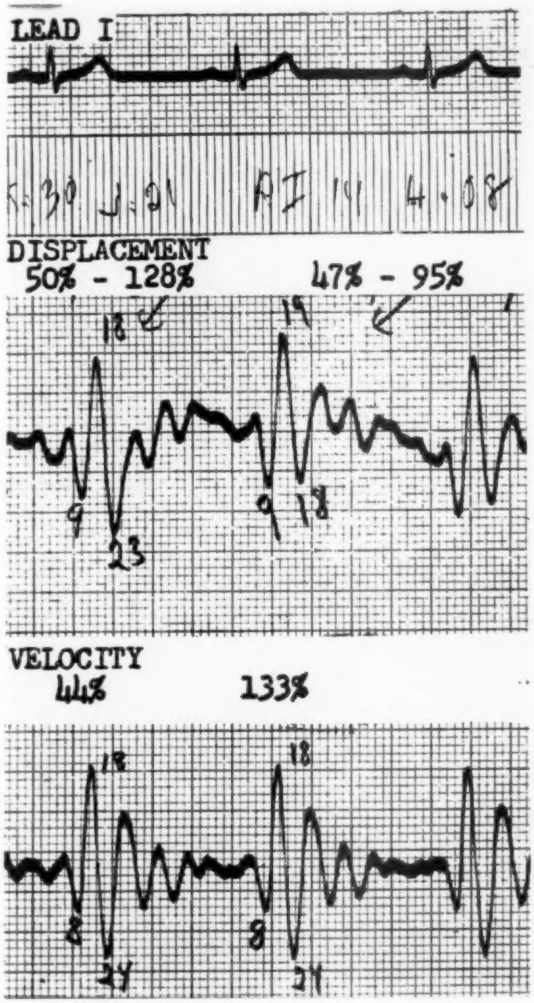

Fig. 3.—A normal 31-year-old pilot. His weight was 156 pounds; height was 72 inches. Body structure was asthenic type. Note that the displacement curve shows deviations even with respiration suspended. The body displacement due to quiet respiration was high (0.005 inch). The amplitude and wave ratios remain constant on the velocity curve.

CASE 4.—A 48-year-old man, with hypertension and mild aortic insufficiency. Blood pressure was 190/76 mm. Hg. These ballistocardiograms show velocity and displacement curves taken simultaneously from the same heart beat. The displacement curves were taken with the Sanborn Photocell with no filter and with the low-frequency filter to straighten the base line. The definite

H-I segments on the velocity tracings are not present on the unfiltered displacement ballistocardiograph. The low-frequency filtered displacement curve shows the H-I segment to a slight extent. Again the timing is rapid, RK = 0.24 seconds, RJ = 0.18 seconds, RI = 0.14 seconds,

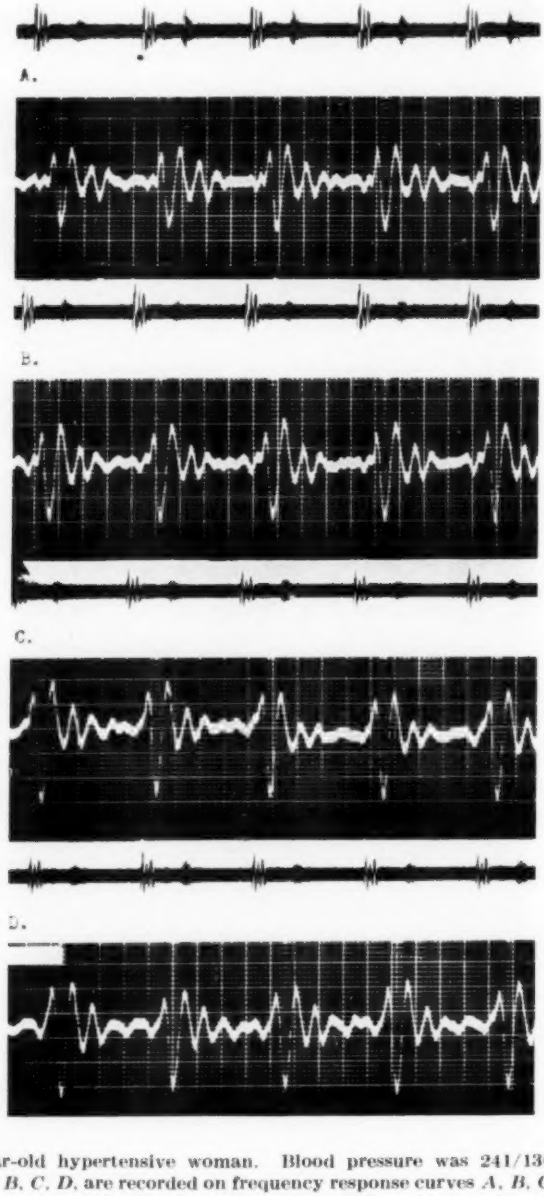

Fig. 4.—A 47-year-old hypertensive woman. Blood pressure was 241/130 mm. Hg. Velocity ballistocardiograms *A, B, C, D,* are recorded on frequency response curves *A, B, C, D,* of Fig. 1. Note the small H-I segment on *A* and *B* with obscuration of the H-I segment on *C* and *D*. This patient has since expired due to a cerebrovascular accident.

and RH = 0.10 seconds. Electrocardiogram shows evidence of tall R waves and a delayed ventricular activation time with slight RS-T segment depression over the left ventricle. Diphasic T wave inversions. (Fig. 5.)

CASE 5.—A 69-year-old man with hypertension. Blood pressure was 230/110 mm. Hg. The patient complained of headaches and had difficulty in walking due to aching and numbness of six years' duration in his legs. Examination revealed no pulsations felt in the femoral arteries; a loud bruit could be heard one inch above the umbilicus; pulsations were felt above this area but none below this area; the abdominal wall was thin, and the obstruction in the abdominal aorta was easily palpable. The etiology of the obstruction was probably due to atheromatous changes in the aorta. The electrocardiogram showed evidence of left ventricular strain and hypertrophy. This man had been treated for essential hypertension for six years. The ballistocardiogram was

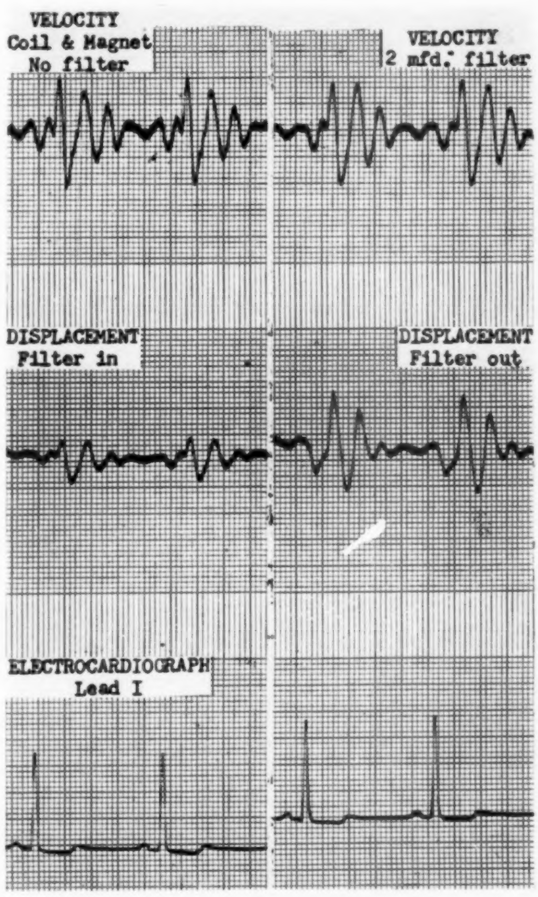

Fig. 5.—A 48-year-old man with hypertension and mild aortic insufficiency. Blood pressure was 190/76 mm. Hg. Note the definite small H-I segment on the velocity curve with no filter. The filtered velocity curve shows the H-I segment also, but the H-I segment is not seen on the photocell. A change in slope only can be seen. Note the pronounced footward deflection, the G valley on all curves.

typical of aortic obstruction. The value of the ballistocardiograph to demonstrate changes in aortic obstruction has been described previously.[5] The deep H-I segment and the short J-K segment are demonstrated in Fig. 6. The displacement curve shows these changes to a more marked degree than the velocity and acceleration curves.*

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*This patient died on Nov. 10, 1952. Autopsy showed a stenosis of the aorta at level of first lumbar vertebra with an intact lumen about 1 cm. in diameter due to marked atheromatous changes.

CASE 6.—A 31-year-old man with typical signs of aortic insufficiency. Blood pressure was 180/20 mm. Hg. Electrocardiograph showed typical left ventricular strain pattern and high voltage R waves over the left ventricle.

The displacement curve showed a deep K wave. The wave form showed no high-frequency components and resembled the deep K seen in some normal lightweight women (Fig. 7).

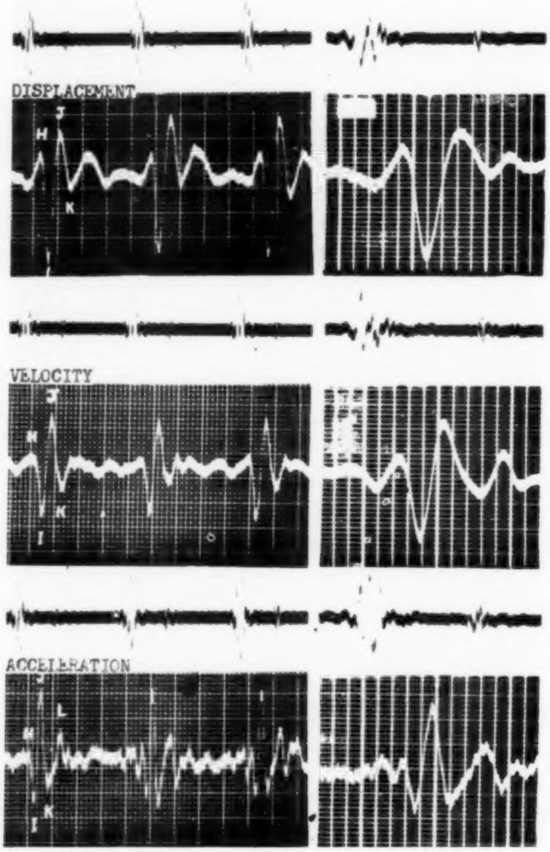

Fig. 6.—A 69-year-old man with hypertension. Blood pressure was 230/100 mm. Hg. Examination showed an obstruction of the abdominal aorta located just above the umbilicus. Note the prominent H wave and deep H-I segment with the short J-K segment on the displacement curve. These findings are less pronounced on the velocity curves and would be obscured on the acceleration curve. Note also the notching of the H wave on the acceleration curve which is the result of a higher frequency component obscured in displacement and velocity.

Fig. 7.—A 31-year-old man with aortic insufficiency, probably rheumatic in origin. Blood pressure was 180/20 mm. Hg. The displacement curve shows no evidence of higher frequency components. The form is typical of displacement curves published in the literature on this condition.[9] The velocity curve *A* was taken on frequency response *C* of Fig. 1. The peak of the J wave is rounded only. Velocity curve *B* was taken on frequency response *B* of Fig. 1. Note the appearance of notching and flattening of the peak of the J with the higher frequency. Acceleration curve *A* was taken on a frequency response flat to 8 cycles with a rapid drop in frequency response starting at 11 cycles. The high-frequency component is midway between the J and K peaks but not sharp. Acceleration curve *B* is taken on frequency response curve flat to 16 cycles with a rapid drop starting at 22 cycles. Note the increase in amplitude of the notched J wave. These high-frequency components of the velocity and acceleration curves are probably of clinical significance.

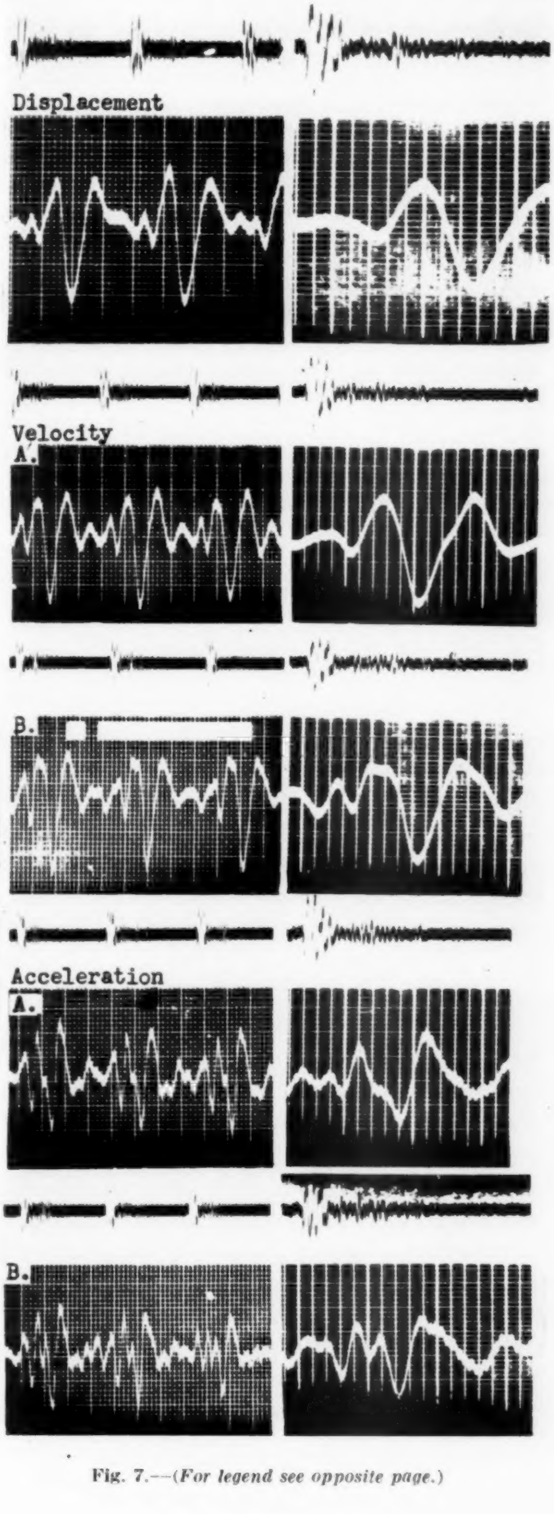

Fig. 7.—(*For legend see opposite page.*)

The velocity curve was typical of our findings in aortic insufficiency, and the deviations from normal have been similar in ten cases to date. The wave ratios of HI to IJ have usually been in the normal range or close to normal.[6] HI of IJ = 69 per cent in this case. However, the percentage relationship of the JK to IJ has been beyond our range of normals in all our cases. JK of IJ = 185 per cent. The velocity curves are taken on frequency response curves *C* and *B*. Note that the flat top of the J wave cannot be seen on frequency response *C*. (Fig. 7, Velocity *A*.) The higher frequency component occurs at the point of maximum turbulence in the sound track recording.

The acceleration curve shows this high frequency component with greater amplitude as a definite notching of the J-K segment. The acceleration curves usually have shown higher frequency abnormalities in valvular disease where turbulence in the flow of blood is present.

In cases of aortic insufficiency, the aortic pressure curve rises steeply and falls rapidly in the latter part of systole giving rise to systolic collapse. Studies by Wiggers[7] show that the chief collapse of the radial pulse in aortic insufficiency occurs during systolic ejection *not during diastole*. Simultaneous central and peripheral pulses have shown that both reach their maximum more rapidly than normally. This is due to the fact that the ventricle under greatly increased initial tension not only ejects a larger systolic volume but delivers most of this during the first half of ejection; thus comparatively less remains to be expelled during the latter half of systole. Then the abrupt collapse, as well as the sudden rise of the radial pulse, is due fundamentally to a redistribution of an increased output during the early and late phases of systolic ejection; hence the systolic collapse is secondarily, not primarily, due to aortic regurgitation.

During systole the notched JK occurs at a point where a higher amplitude is noticed over the heart sound murmur. It is probable that this notching phenomena is related to early systolic collapse.

DISCUSSION

In normal adults the fundamental frequency components seem to be in the region of 1 to 8 cycles per second; therefore, it is our contention that instrumentation used should have a flat response in this range. However, to show properly aortic obstruction or coarctation the displacement frequency response should be flat to below one-half cycle. The filters used to straighten base line deviations due to respiration obscure the coarctation effect.

The use of velocity measuring devices has been of greatest value in measurements of wave ratios as the standards for normal individuals show the least deviations. The HI and JK expressed as a percentage relationship of the IJ are much closer when measured as velocities rather than displacement or acceleration. The reason for this is obvious when one looks at the frequency response curve in Fig. 1. The scatter of natural frequencies of the body from 3 to 7 cycles (as measured by the head-push technique) show changing amplitudes of wave segments with frequency when measured as displacement and acceleration.

Velocity measurement with flat response to higher frequencies, however, cannot always be used due to high amplitude ambient vibrations (tremors), and we have found it necessary to use filters in many cases. This is especially true in the older age groups and in coronary heart disease as the signal-noise ratio is decreased due to low amplitude velocity signals. In the use of filters we have found that a filter that shows a flat response to at least 8 cycles shows the least distortion of wave ratio measurements when compared to those derived from an unfiltered coil and magnet in young normal adults. However, for timing purposes it is imperative to use an unfiltered velocity signal due to signal delay associated with filter networks.

In the use of acceleration as a clinical measurement, it is absolutely essential to have frequency discrimination at the higher frequency level as ambient factors at higher frequencies are emphasized. The acceleration curves that are demonstrated have been measured on a flat acceleration response to 16 cycles with a rapid drop in response starting at 22 cycles. It becomes increasingly difficult to work with acceleration curves that are flat to above 20 cycles. For clinical use we believe that the flatness of response criteria should be not above 20 cycles with a rapid drop in response above this point.

The pressing need in ballistocardiography for standardized amplitudes should be apparent. This problem has been solved, and the techniques for standardizing velocity in millimeters per second will be published.[8]

SUMMARY AND CONCLUSIONS

1. The need for standardized techniques for ballistocardiography has been discussed.

2. The relationship of displacement, velocity, and acceleration to the body motion complex with their effect on frequency response has been presented.

3. The need for multiple frequency response characteristics to study adequately various cardiovascular conditions has been presented.

4. Ideal instrumentation in ballistocardiography should measure: (a) displacement with frequency response flat to one-half cycle to show abnormalities of aortic circulation; (b) velocity with a flat response (as a coil and magnet) to study high-frequency components, wave ratios, and timing, and with a filter flat to 8 cycles to use in cases of high amplitude body tremor, and (c) acceleration with a flat response to 16 to 20 cycles per second and rapid rolloff filters to show more adequately high-frequency abnormalities in coronary disease and especially in valvular diseases where turbulence of blood is present.

5. Standardization of velocity as an absolute measurement as millimeters per second is desirable.

REFERENCES

1. Starr, I., and Schroeder, H. A.: Ballistocardiogram II. Normal Standards, Abnormalities Commonly Found in Diseases of the Heart and Circulation and Their Significance, J. Clin. Investigation **19**:437, 1940.
2. Nickerson, J. L.: The Low Frequency Critically Damped Ballistocardiograph, Federation Proc. **4**:201, 1945.
3. Dock, W., and Taubman, F.: Some Techniques for Recording the Ballistocardiogram Directly From the Body, Am. J. Med. **8**:6, 751, 1949.
4. Greenough, M. L.: Technical Details of the Electronic Micrometer, Electronics, 1947, p. 172.
5. Nickerson, J. L.: J. Clin. Investigation, **78**:369, 1949.
6. Smith, J. E., and Bryan, S.: The Low Frequency Velocity Measurement Ballistocardiograph, Circulation **5**:6, 892, 1952.
7. Wiggers, C. J.: Physiology in Health and Disease, ed. 4, Philadelphia, 1944, Lea & Febiger, p. 738.
8. Smith, J. E.: A Calibrated Bar Magnet Velocity Meter for Use in Ballistocardiography, Am. Heart J. **44**:872, 1952.
9. Jones, R. J., and Goulder, N. E.: An Empiric Approach to the Interpretation of the Low Frequency Critically Damped Ballistocardiograph, Circulation **2**:5, 756, 1950.

A NEW FULL-FREQUENCY RANGE CALIBRATED BALLISTOCARDIOGRAPH. I.

Recording the Body Ballistics in Displacement, Velocity, and Acceleration

Sidney R. Arbeit, M.D., and Norman Lindner, M.S. in M.E.

Jersey City, N. J.

THE BALLISTOCARDIOGRAM is a record of the transient motion of the body during cardiac systole.[1] The motion of this damped spring-mass system (the body) is caused by the internally impressed force derived from the cardiac propulsive effort. In turn, it is possible to derive the value and shape of this impressed force if the resultant motion can be seen in terms of its principal functions—displacement, velocity, and acceleration.[2] We will present and discuss the equipment necessary to derive this information and suggest minimum standards for sensitivity and frequency response.

It is hardly possible to list (and certainly not possible to describe) in this article all the individual forms of electric gauging equipment. All ballistocardiographs have the same functional parts: (1) a mechanical system which responds to the motion being measured, frequently called a "pickup" or a sensing system; (2) a coupling system, and (3) a recording and timing-device, usually an electrocardiograph or a cathode-ray oscillograph.

I. *The Pickup.*—Different types of pickup systems are used. These are (A) directly connected systems; (B) electromagnetic air couplings; (C) photoelectric, and (D) seismic systems.

A. A "directly connected" pickup system usually consists of a casing from which a probe protrudes.[3] The end of the probe, which is inside the case, is usually connected to the case through a spring. In use, the free end of the probe is put in contact with the vibrating body and the case is pushed down, distorting the spring so that the probe is held against the moving body. The case is attached to some neighboring body which is not vibrating. The relative motion between the probe and the case is an exact reproduction of the motion measured as long as the probe remains in contact with the moving body.

B. Electromagnetic induction systems are capable of sensing velocity only. A coil is attached to the body and moves in the field of a magnet which is fixed to the table (or vice versa). Current generated in the coil is directly proportional to the velocity of the motion being measured.

C. Photoelectric devices operate by placing a light source on the moving body and projecting a beam of light onto a photoelectric cell. Motion of the body varies the quantity of light which will impinge on the cell, generating current directly proportional to the motion. This type of device measures displacement.

D. Seismic pickup[1] systems get their name from the fact that they are constructed on the principle of the seismograph used to measure earthquake motions. This type of instrument consists of a case containing a mass which is suspended from the case by springs. The case is firmly attached to the vibrating body and moves with it. The upper end of the mass suspension

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spring moves with the case and this excites the suspended mass into motion. The relative difference in motion between the vibrating case and the spring-suspended mass is measured. If the mass is heavy enough, the suspension spring soft enough, and the frequency of the measured motion high enough, the mass stands almost still in space and the relative motion between the case and the mass is an almost exact reproduction of the motion being measured. If the mass is light enough, the suspension spring stiff enough, and the frequency of measured motion low enough, the mass almost follows the motion of the case. The small relative motion that exists between the case and the mass is almost exactly proportional to the instantaneous acceleration of the case. We have dealt at length with this principle because theoretically the accelerometer would for many reasons be an ideal ballistic sensing unit. Unfortunately, we are measuring acceleration (around 0.005 g) far beyond the range of any commercial units. We have been unable to interest any manufacturer in producing an experimental device of the required sensitivity. However, since the velocity pickup system is remarkably accurate, it is practical to derive acceleration from such a (velocity) system. The electrical differentiation of acceleration from velocity can be more accurate than the actual acceleration measuring devices.

II. *Coupling and Transmitting.*—Relative motion is sensed by the pickup unit and transmitted to an indicating or recording device. It may be amplified or magnified in the transmitting mechanism. This amplification can be mechanical, optical, or electrical.

Mechanical transmissions, making use of levers and gears, are too crude for the purpose of accurately measuring and recording the very small motion that we deal with.

Optical transmissions make use of mirrors on spindles, with the main amplification in the optical lever. In general, they lack the versatility of the electrical methods and the ruggedness of construction necessary for the portable ballistocardiograph.

The electrical methods make use of changing resistance, inductance, or capacitance by the differences in the relative motion between the pickup members. The impulse so derived can be passed through electrical networks to be amplified, differentiated, or integrated.

Rigid standards must be established for this coupling network. Its frequency response must be flat in the range of measured ballistic motion. It must not do partial differentiation or integration that will result in a hybrid tracing. It must have no time shifts (delays or advances). If there is diagnostic information in the form, amplitude, and timing of these curves, an error introduced at this point will interfere with the successful establishment of normal values.

III. *Recording.*—The electrocardiograph is the usual recording instrument available to all who are interested in ballistocardiography, and is well suited to record the body ballistic curves.

INSTRUMENTATION. MINIMUM STANDARDS

Having agreed to study these phases and functions of position (displacement, velocity, and acceleration), we then consider the choice of equipment.

A. *Displacement.*—From the hundreds of displacement-sensing devices available, we can pick many that are accurate and physically adaptable to our purpose. We would like our pickup to sense motion from 0.00001 inch up to 0.004 inch with an error of less than 2 per cent of maximum and to be absolutely linear in response between 0.0001 and 0.002 inch. In addition, the device must be both easy to handle and simple to apply. All of these qualities are available in suitably chosen pickups. It has now become customary to accept an amplitude of 15 mm. as normal on the displacement tracing. It would seem then that the best standardization of actual motion to recorded motion calls for a gain of about 700, so that 0.0025 cm. records as 1.75 cm. (0.001 inch as 0.7 inch). This information should be furnished with each piece of equipment so that it will be possible to compare amplitudes of ballistic waves and patterns no matter how taken. It will then be possible to establish tables of standards for deriving the force necessary to cause such displacements.

Displacement curves also may be obtained by electrical integration from velocity.[5] This, of course, depends on the accuracy of the velocity pickup and the integrating network, and may be remarkably precise. However, the theoretical laws governing the displacement pickup are more exact than those governing the sum of the velocity pickup, plus electrical integration, and plus the electrical amplification. Therefore, it would seem more desirable to sense displacement directly.

B. *Velocity.*—Velocity-measuring devices present few problems. Properly designed, the velocity pickup is a theoretically perfect instrument. A coil is moved in a magnetic field. So long as the magnetic field is of the same density throughout the range of the motion of the coil, the output of the pickup will be directly proportional to the velocity of the motion. This is true providing the coil is moved in a fixed, performed field whose flux lines are parallel throughout the entire range of the motion of the coil. Velocity pickups that operate in fringe flux are inherently inaccurate.

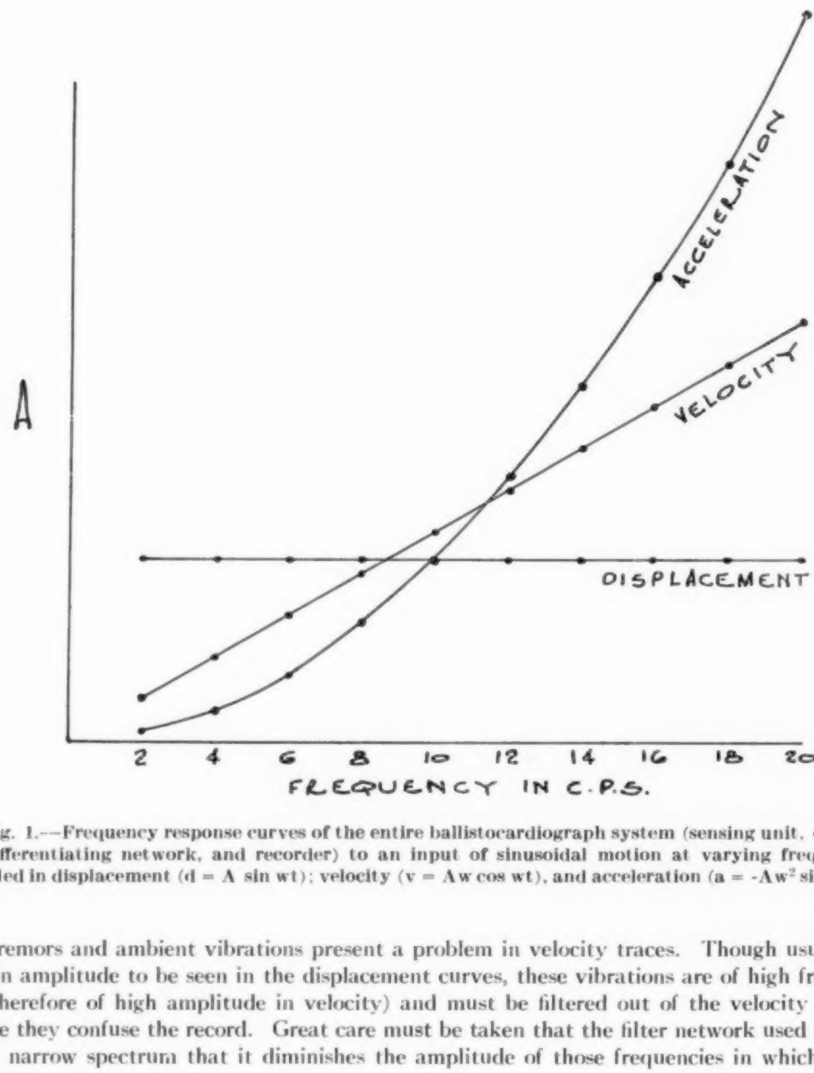

Fig. 1.—Frequency response curves of the entire ballistocardiograph system (sensing unit, coupling, and differentiating network, and recorder) to an input of sinusoidal motion at varying frequencies.[8] Recorded in displacement (d = A sin wt); velocity (v = Aw cos wt), and acceleration (a = -Aw^2 sin wt).

Tremors and ambient vibrations present a problem in velocity traces. Though usually too small in amplitude to be seen in the displacement curves, these vibrations are of high frequency (and therefore of high amplitude in velocity) and must be filtered out of the velocity tracings because they confuse the record. Great care must be taken that the filter network used is not of such a narrow spectrum that it diminishes the amplitude of those frequencies in which we are interested.

Velocity tracings may be obtained also by electrically differentiating the output of a displacement pickup. This can be done quite accurately. However, the more accurate a differentiating network is, the greater its voltage loss. This means that amplifiers will have to be added to boost this voltage up to the range required to activate the recorder. It would seem best to avoid this problem at this stage and to sense velocity directly. If velocity is already a differen-

tiated curve, that is, it is derived from displacement, and it later becomes necessary to derive acceleration from velocity, then we will have double differentiation and double amplification to get acceleration. Obviously, the chances of error and increased noise are multiplied.

Standardization of a velocity tracing is a more difficult problem. Lower frequencies (1 to 2 cycles per second), regardless of their amplitude, are not seen in this ballistic record. The absence of response at this frequency range is no drawback; it merely eliminates undesired respiration waves. At the other end of the frequency spectrum, ambient vibrations do present a problem

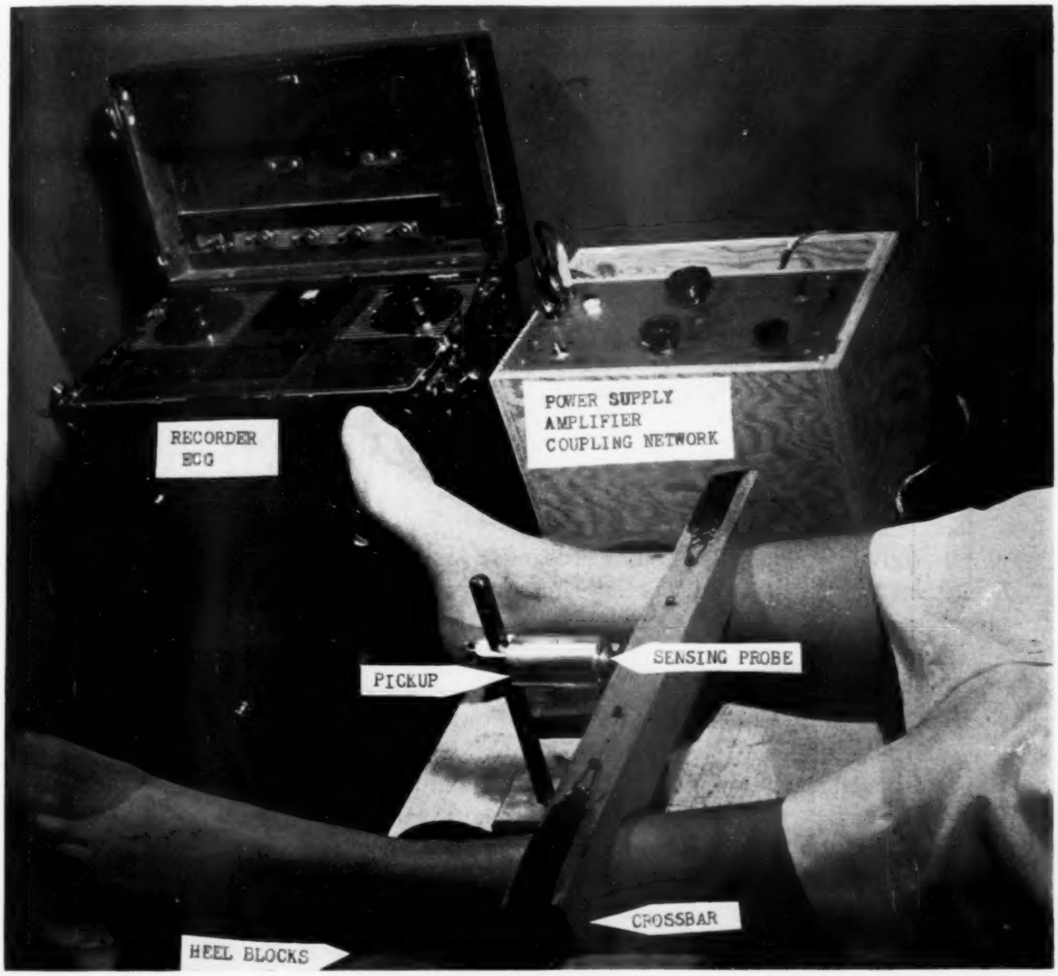

Fig. 2.—The displacement, velocity, and acceleration ballistocardiograph.

in velocity and acceleration traces. In order to eliminate the distortion introduced by these body tremors and ambient vibrations, we will probably have to limit ourselves to the study of velocities below 20 cycles per second. Empirically, then, we can adjust our circuits so that a frequency of 6 cycles per second at 0.001 inch delivers 1½ millivolts to our recorder. Then, without altering the sensitivity of the electrocardiograph machine, our velocity tracing in the normal subject will be comparable in total amplitude to the amplitude of the displacement curve. The actual standardization will then be 0.1 mm. per second recorded as 1.5 mm. total amplitude.

C. *Acceleration.*—Although the ideal seismic instrument for sensing acceleration can be mathematically defined, a source of error would still exist in the very theory of the seismograph. In view of this objection, it appears at the moment that there is less danger of distortion to the acceleration wave form if it is derived by electrical differentiation from velocity rather than by sensing it directly. There is less source of error in single electrical differentiation than there is in poor design and application of an accelerometer.

In order to maintain the average amplitude of the normal acceleration wave at 15 mm. (the average maximum amplitude of the displacement curve in the normal) we have to adjust the output of the acceleration pickup and electrical network so that 6 cycles per second^2 at 0.001 inch (0.0025 cm.) peak to valley displacement will deliver 1.5 millivolts. The electrocardiograph, still at the 1 cm. per mv. standardization, will record this as 1.5 cm. This corresponds to the absolute relationship of 3.5 mm. per second squared acceleration recorded as 1.5 mm.

Since acceleration is derived from velocity, its maximum frequency response will be the same as that of the velocity system. In our experience it is essential that this frequency response be maintained absolutely flat to ***not less than 20 cycles per second.*** Many of our tracings show what we believe to be important information at the upper limits of this range.

D. *The "R" Wave.*—It is impossible to overestimate the necessity of a reference timing point in the ballistic record. Unless the three functions of position are simultaneously recorded, means must be provided for synchronizing them. Without this, the information in the curves will not be available for use in the equation for solution of force. The introduction of a "pip" or "R" wave of the electrocardiogram can readily be accomplished. There may be objections to the use of this "R" wave, since it may vary in time in different leads. This would mitigate against its use in determining standards for ballistic RI and RJ intervals. Actually these variations in time are very small compared to the time range of the ballistocardiogram. In addition, if the same electrocardiographic lead is used on all three curves (displacement, velocity, and acceleration), then the "R" wave as a reference timing point would exactly relate the events being measured. For this reason we have incorporated a means for printing the "R" wave in ballistocardiograms.[6]

In summary, the clinical ballistocardiograph described above will give us displacement, velocity, and acceleration curves. Displacement will be directly sensed, critically accurate, and directly inscribed. Velocity will be directly sensed, and frequencies above 20 cycles per second will be filtered out without affecting the amplitude of those below it. Acceleration will be derived by single electrical differentiation from velocity without further filtering. The "R" can be electrically inscribed.

The ballistocardiograph presented here conforms to these minimum standards. The tracings were taken on a conventional office examining table in a wooden frame building. The displacement, velocity, and acceleration curves reproduced are better than 95 per cent accurate reproductions of the absolute values of these functions for frequencies between 2 and 20 cycles per second. This means, of course, that the nominal cut-off frequencies (70 per cent points) are outside this range. In dealing with a narrow band of low frequencies such as these, we do not believe that nominal cut-off points are sufficiently accurate to describe the responses of the system.

CASE REPORTS

CASE 1 (Fig. 3). *Normal Ballistocardiograph.*—The displacement, velocity, and acceleration curves in the normal ballistocardiograph are very similar in form and amplitude though quite different in timing. The similarity in form derives from the nature of the physical system and the forces involved. The similarity in amplitude is dependent upon the same physical considerations plus the arbitrary standardizations of these traces. The difference in timing is dependent largely

on the phase rotation of successive derivatives (note that K_a is 180 degrees out of phase with J_d at the same instant). Other factors that may affect the timing are (1) out of phase application of force (in the abnormal ballistocardiograph); (2) variations in damping characteristics, and (3) instrumentation error.

The heavy vertical line in the expanded trace is a simultaneous time line measured from "R."

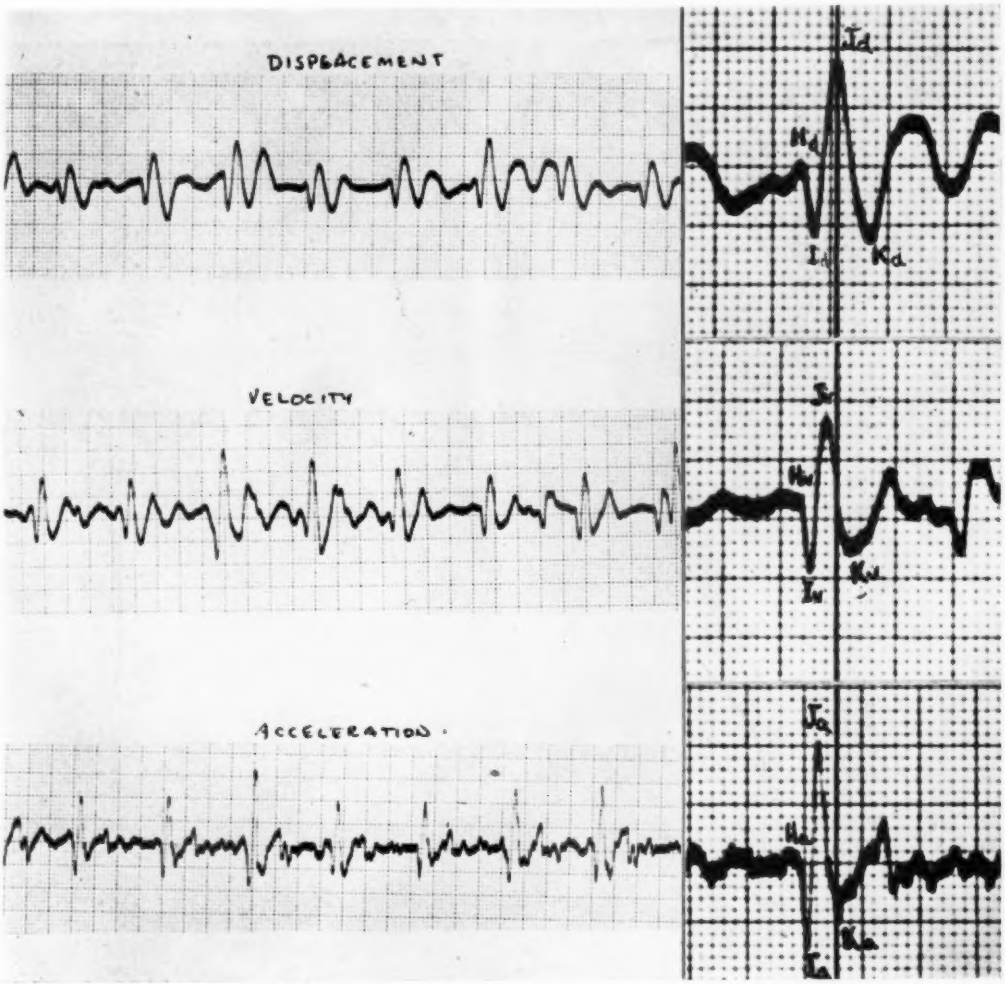

Fig. 3.—(See report, Case 1).

CASE 2 (Fig. 4). *Rheumatic Heart Disease.*—A 44-year-old woman had rheumatic heart disease, mitral stenosis and insufficiency, enlarged left auricle, and no ventricular enlargement. The displacement curve shows a deep but slowly developed I wave and a small sharp notch in the K wave. If explained in terms of a spring mass system of 5 cycles per second natural frequency the I is formed by a large total energy applied at a rate below the natural frequency of the system. The notch in K is formed by two sharply applied opposing forces whose frequencies are above the natural frequency of the body. This means that the time duration of each force is small compared to the time required for one cycle of motion at the natural frequency and that the time interval between the forces is also small compared to this same interval.[7] Then, in successive differentiations the low-frequency force progressively decreases or disappears, and the high-frequency force

progressively increases in amplitude. In acceleration the I_a has disappeared and the 1 mm notch of K_d is separated into its three components with an average amplitude of over 10 mm. If in displacement this latter defect is labeled a notched K then in acceleration these three parts should be labeled $1L_a$, $2L_a$, and $3L_a$.

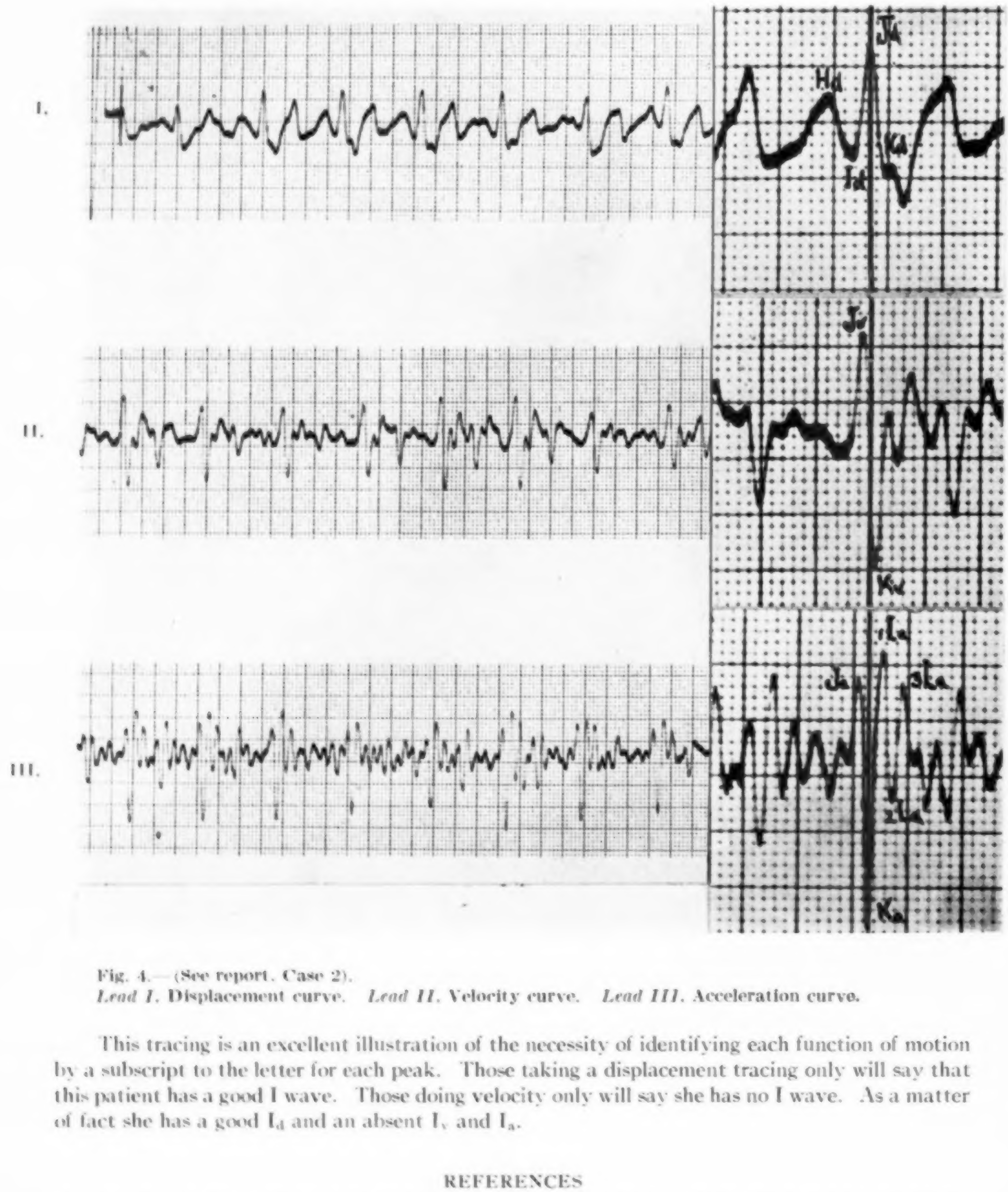

Fig. 4.—(See report, Case 2).
Lead I. **Displacement curve.** *Lead II.* **Velocity curve.** *Lead III.* **Acceleration curve.**

This tracing is an excellent illustration of the necessity of identifying each function of motion by a subscript to the letter for each peak. Those taking a displacement tracing only will say that this patient has a good I wave. Those doing velocity only will say she has no I wave. As a matter of fact she has a good I_d and an absent I_v and I_a.

REFERENCES

1. Gordon, J. W.: On Certain Molar Movements of the Human Body Produced by the Circulation of the Blood, J. Anat. & Physiol. **11**:553, 1877.
2. Slater, J. C., and Frank, N. H.: Introduction to Theoretical Physics, New York, 1933, McGraw-Hill Book Company, pp. 27-35.

3. Roberts, H. C.: Mechanical Measurement by Electrical Methods. Pittsburgh, Pa., 1946, Instrument Publishing Co., Inc.
4. Hetenyi, M.: Handbook of Experimental Stress Analysis, New York, 1950, John Wiley & Sons, Inc., p. 316.
5. Greenwood, I. A., Jr., Holdan, J. V., Jr., and Macrae, D., Jr.: Electrical Instruments, New York, 1948, McGraw-Hill Book Company, p. 78.
6. Gubner, R.: Circulation **4**:239, 1951.
7. Timoshenko, S.: Vibration Problems in Engineering, New York, 1937, D. Van Nostrand Company, Inc., p. 44.
8. Frayne, J. B., and Wolfe, H.: Elements of Sound Recording, New York, 1949, John Wiley & Sons, Inc., p. 22.

A SIMPLE METHOD TO OBTAIN AN APPROXIMATE VECTOR-CARDIOGRAM WITH AN ORDINARY ELECTROCARDIOGRAPH

Frontal and Horizontal Planes

Carlos Ayala y de Landero

Guadalajara, Mexico

After obtaining a series of electrical instantaneous and successive axes with the ordinary electrocardiogram, one can obtain a vectorcardiogram by joining the ends of those vectors with a line.

PROPOSED METHOD

I. To find direction of instantaneous vectors:

A. *Frontal plane.*—My proposed method[1] may be used, as well as any other which gives the best possible exactitude.

B. *Horizontal plane* (Fig. 1).—If precordial Leads V_2 and V_6 are used, lines representing them may be considered perpendicular to each other. One can obtain direction of the electrical instantaneous axis in the horizontal plane with the help of the following formula:

$$\text{Tan } X = \frac{V_2}{V_6}$$

To simplify the foregoing procedure, Table I, which was obtained by application of the formula in 400 theoretical cases with values for both leads from $+10$ to -10, may be used.

II. After finding the direction, the magnitude of the vectors can also be found:

A. *Frontal plane.*—For this purpose formulas proposed by Einthoven,[2] $E = e_1/\cos X$, $E = e_2/\cos (X\text{-}60)$, may be used. In these formulas, E represents the magnitude of the resulting vector, e_1 and e_2 represent the projection of that vector upon lines representing Leads I and II, and X represents the angle which indicates the direction of the vector.

By applying the foregoing formulas Table II was obtained. This table contains results expressed in units similar to those chosen to measure Leads I and II.

From the Gabinete de Cardiología y Nefrología del Hospital Civil de Guadalajara, México. Facultad de Medicina de la Universidad de Guadalajara, México.

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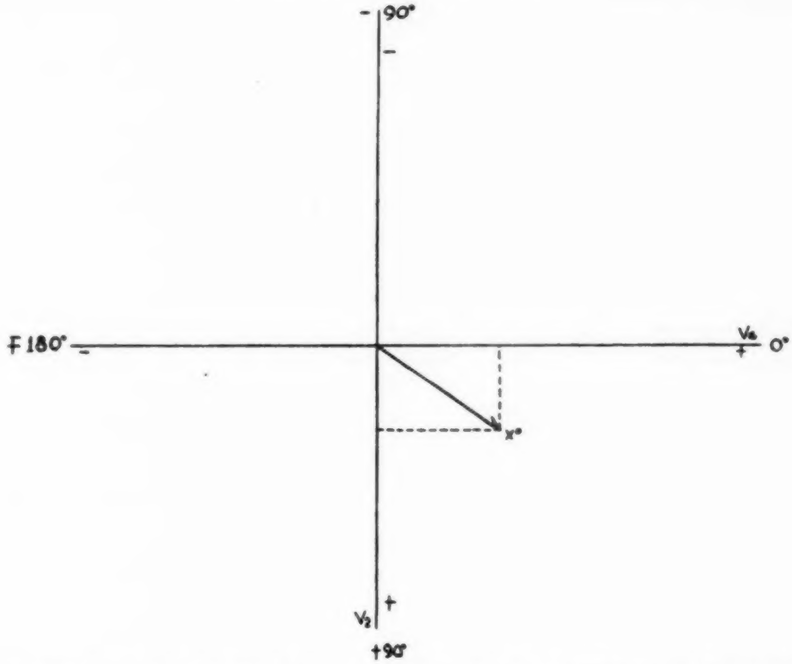

Fig. 1.—Horizontal plane seen from above. Positive values of V_6 are inscribed on the left-hand side of the center line, and the positive values of V_2 are inscribed on the anterior part of the center line.

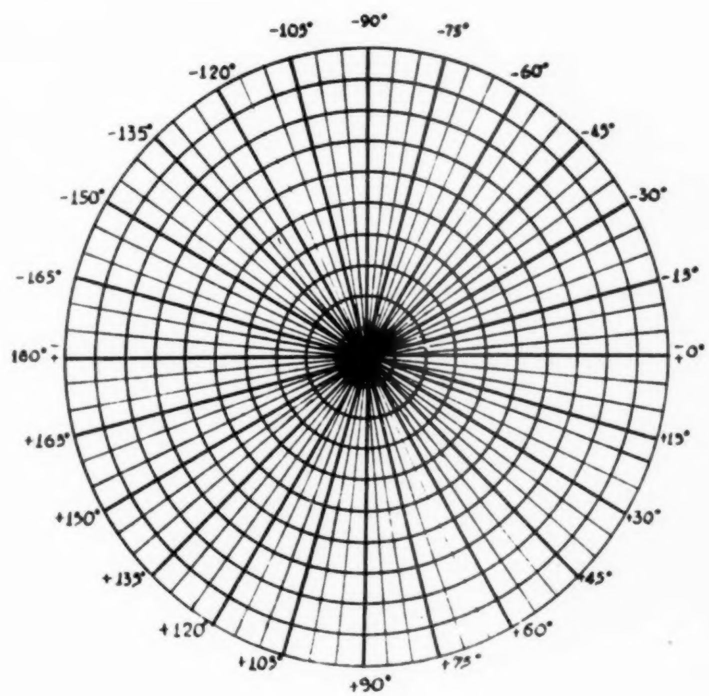

Fig. 2.

TABLE I.

V_2	V_6																			
	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
1	174	174	173	172	171	169	166	162	153	135	45	27	18	14	11	9	8	7	6	6
2	169	167	166	164	162	158	153	146	135	117	63	45	34	27	22	18	16	14	13	11
3	163	162	159	157	153	149	143	135	124	108	72	56	45	37	31	27	23	21	18	17
4	158	156	153	150	146	141	135	127	117	104	76	63	53	45	39	34	30	27	24	22
5	153	151	148	144	140	135	129	121	112	101	79	68	59	51	45	40	36	32	29	27
6	149	146	143	139	135	130	124	117	108	99	81	72	63	56	50	45	41	37	34	31
7	145	142	139	135	132	126	120	113	106	98	82	74	67	60	54	48	45	41	38	35
8	141	138	135	131	127	122	117	111	104	97	83	76	69	63	58	53	49	45	42	39
9	138	135	132	128	124	119	114	108	103	96	84	77	72	66	61	56	52	48	45	42
10	135	132	129	125	121	117	112	107	101	96	84	79	73	68	63	59	55	51	48	45

Table obtained with V_6 (in the top line) and V_2 (in the left column). Results are expressed by degrees, positive when V_2 is positive too, and vice versa.

TABLE II.

LEADS V_6 AND I	ANGLE X 0°	5°	10°	15°	20°	25°	30°	35°	40°	45°	50°
1	1	1.004	1.015	1.035	1.064	1.103	1.155	1.221	1.305	1.414	1.556
2	2	2.008	2.031	2.071	2.128	2.207	2.309	2.441	2.611	2.828	3.111
3	3	3.011	3.046	3.106	3.192	3.310	3.464	3.662	3.916	4.243	4.667
4	4	4.015	4.062	4.141	4.257	4.413	4.619	4.883	5.222	5.657	6.223
5	5	5.019	5.077	5.176	5.321	5.517	5.774	6.103	6.527	7.071	7.778
6	6	6.023	6.093	6.212	6.385	6.620	6.928	7.324	7.833	8.485	9.334
7	7	7.027	7.108	7.247	7.449	7.724	8.083	8.545	9.138	9.899	10.890
8	8	8.031	8.123	8.282	8.513	8.827	9.238	9.765	10.444	11.314	12.445
9	9	9.034	9.139	9.318	9.577	9.930	10.393	10.986	11.749	12.728	14.001
10	10	10.038	10.154	10.353	10.642	11.034	11.547	12.207	13.055	14.142	15.557
	180°	175°	170°	165°	160°	155°	150°	145°	140°	135°	130°

LEADS V_6 AND I	ANGLE X 55°	60°	65°	70°	75°	80°	85°	LEAD II	ANGLE X 90°	LEAD V_2	ANGLE X 90°
1	1.743	2	2.369	2.924	3.864	5.760	12.271	1	1.155	1	1.004
2	3.487	4	4.738	5.848	7.728	11.521	24.541	2	2.309	2	2.008
3	5.230	6	7.107	8.772	11.592	17.281	36.812	3	3.464	3	3.011
4	6.973	8	9.476	11.696	15.456	23.041	49.083	4	4.619	4	4.015
5	8.717	10	11.844	14.620	19.320	28.802	61.353	5	5.774	5	5.019
6	10.460	12	14.213	17.544	23.184	34.562	73.624	6	6.928	6	6.023
7	12.204	14	16.582	20.468	27.048	40.323	85.894	7	8.083	7	7.027
8	13.947	16	18.951	23.392	30.912	46.083	98.165	8	9.238	8	8.031
9	15.690	18	21.320	26.316	34.776	51.843	110.436	9	10.393	9	9.034
10	17.433	20	23.689	29.240	38.640	57.604	122.706	10	11.547	10	10.038
	125°	120°	115°	110°	105°	100°	95°		90°		90°

Table II was obtained with Leads V_6 and I (in the left column) and with possible direction of electrical axis expressed by angles (in the top and down line); in cases where X = 90 degrees Leads II and V_2 were used by reason that being X = 90 degrees Leads I and V_6 did not have projection of electrical axis. The signs of leads and angle X are disregarded, because the sought results are absolute values.

B. *Horizontal plane* (Fig. 1).—The magnitude of electrical instantaneous axis may be calculated either by the application of formulas: $E = V_6/\cos X$, $E = V_2/\sin X$, or by using Table II.

III. After obtaining a chosen variable number of instantaneous vectors, their ends will be joined by a line to obtain a vectorcardiogram.

IV. To facilitate the above procedures, a diagram (Fig. 2) may be used. The diagram consists of graduated radii separated from each other by angles of 5 degrees, crossed by a series of concentric circles, the distance of these concentric circles being 0.5 cm. from one another (the distance in question may be greater or lesser than 0.5 cm.; here it has been used arbitrarily).

By placing a sheet of copy paper on the diagram, ends of instantaneous vectors will be obtained. The graduated radii will indicate the direction, and the concentric circles will indicate the magnitude.

SUMMARY AND CONCLUSIONS

A simple method for obtaining an approximate vectorcardiogram by applying the commonly used leads is presented. The method suggested is only applicable to frontal and horizontal planes.

A common lead for both planes does not appear; therefore, they will be obtained separately.

The best approximation of the results depends upon the number of instantaneous electrical axes taken into consideration; for this purpose electrocardiographic complexes and waves may be widened by modifying the speed of the running of the paper. For best approximation Lead V_6 must be taken at the same level as Lead V_2.

REFERENCES

1. Ayala y de Landero, C.: A Mathematical Method to Determine Electrical Axis Direction of Electrocardiographic Waves, Am. Heart J. **44**:67, 1952.
2. Einthoven, W.: On the Direction and Manifest Size of the Variations of Potential in the Human Heart and on the Influence of the Position of the Heart on the Form of the Electrocardiogram, Am. Heart J. **40**:163, 1950.

MEAN SPATIAL VECTORCARDIOGRAPHY. THE NORMAL QRS AND T VECTORS

DAN L. URSCHEL, M.D., AND DENTON C. ABBEY

MENTONE, IND.

THE METHOD of vector analysis of the conventional cardiogram which was originated by Grant[1,2,3] has proved of value in clarifying our understanding of the electrical forces involved in cardiac action. Vectorcardiography itself dates back to the first work with the electrocardiogram, as Einthoven's mean electrical axis was a presentation of the frontal plane projection of what is now called the mean spatial QRS vector. Einthoven represented this as a vector in his original publications. However, the term "vectorcardiography" was soon applied to what is now called the QRS loop or vectorcardiogram, and the subject became hidden in a maze of higher mathematics, arguments as to electrode placement, discussions regarding the validity of various hypotheses, etc. This type of work has been, and still is, necessary, and many of the original problems have been solved. However, this approach served to thoroughly confuse the average physician interpreting routine cardiograms, and as a result a useful teaching tool was neglected until Grant published his pioneering approach.

There has been criticism of his work on several grounds. Such criticism usually takes one of several forms. Inasmuch as he uses only the standard leads which are available to all, it has been stated that he is doing nothing new. Other criticisms are tied in with the old arguments about the validity of the Einthoven hypotheses, and of the Wilson central terminal, as the method is based on the assumption that these theories are essentially correct. It has been stated that the method is crude, lacking in scientific accuracy. It is not within the scope of this paper to present the research upon which Grant based his work, but the reader who is especially interested is referred to the above references, as well as to subsequent publications by Grant and his associates.[4,5] Suffice it to say at this time that the method appears well grounded in basic theory, and the validity of the method has been well documented.

In the first criticism listed above lie both the weakness and the strength of this work. Because the method uses only the standard leads, no information is made available which is not already there for interpretation by the skilled electrocardiographer. However, and this is the great advantage of this approach, Grant has reduced the many variations of the QRS-T complex to a few simple measurements. The student who learns his electrocardiography by this method

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does not have to memorize complexes without a proper understanding of the underlying reasons for such tracings. Using this, he can visualize the forces involved in any portion of the cycle and can understand why abnormalities in such forces produce certain alterations in the electrocardiogram. It is, in essence, a simplified visual approach to the electrical forces producing electrocardiograms.

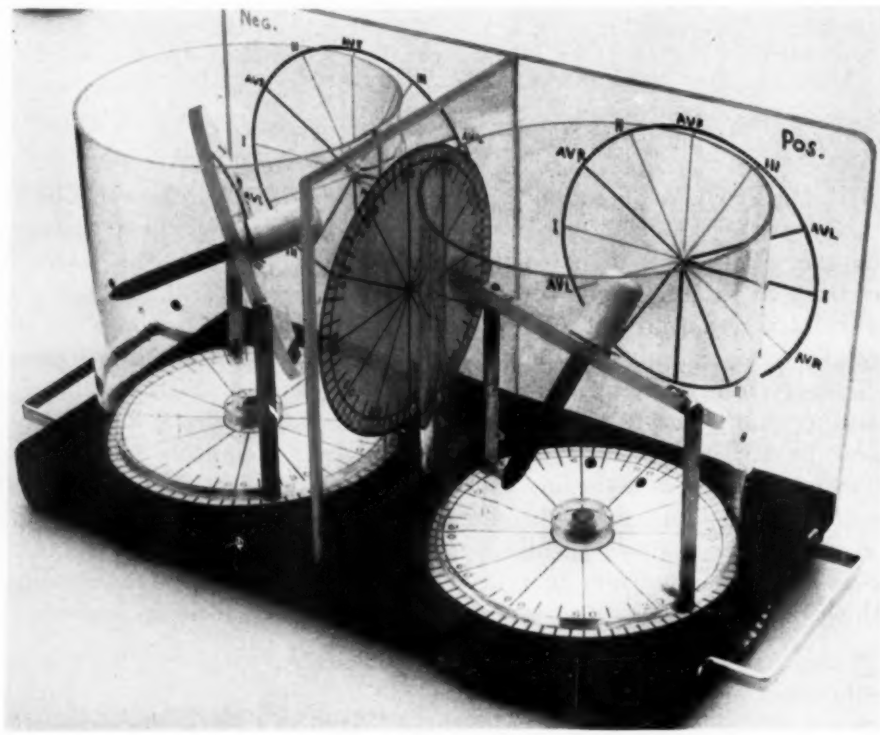

Fig. 1.—The model used by the authors in calculating and demonstrating the mean spatial vectors.

Because this is a visual approach, many models have been devised to demonstrate the spatial characteristics of the mean vectors. Grant and Estes[5] have illustrated one such model in their monograph on the method. We have modified this by the addition of horizontal and sagittal scales which enable one to mathematically record the spatial characteristics of the vectors.[6] Robertson,[7] in a recent publication has made a plea for consistency of sign and of method in vectorcardiography. In accordance with his suggestions we have attempted to pattern our model along the lines of most common usage. We use the hexaxial reference system for the frontal plane. The sagittal plane is viewed from the left of the patient, as the apex of the heart lies on this side, and abnormalities of position of the apex are thus best demonstrated. We have not followed Robertson's nor Grant's usage in representing the horizontal (or as previously labeled, coronal) plane. They feel that this should be represented as being seen from below, because it has been common usage to refer to rotation of the heart about its long axis as if it were viewed from the apex, or below. However, in this work we are not concerned with rotation in this axis alone, but in electrical position of

the heart in a true horizontal plane. In constructing our model we therefore mounted the reference scale at the bottom of the "chest," and record the vectors as if viewed from above. In our opinion it is much easier to visualize the forces and the electrode positions, in this manner, although there is no apparent theoretic reason why our method is better or worse than the other. Our model is shown in Fig. 1, and it may be seen to be double-barreled, or made up of two identical cylinders, or chests. This dual apparatus is not necessary for demonstrating any single vector, but is of assistance in calculating the QRS-T angle, which is of great importance in interpreting abnormalities in the T wave.[4] In Fig. 2 we have shown the reference scales which are used in recording the position of the vectors. As stated, the horizontal (coronal) scale is identical to one mounted in the base of the model, the sagittal scale to one mounted between the chests. The frontal plane scale is the hexaxial reference system, which is also engraved on the plastic behind the chests.

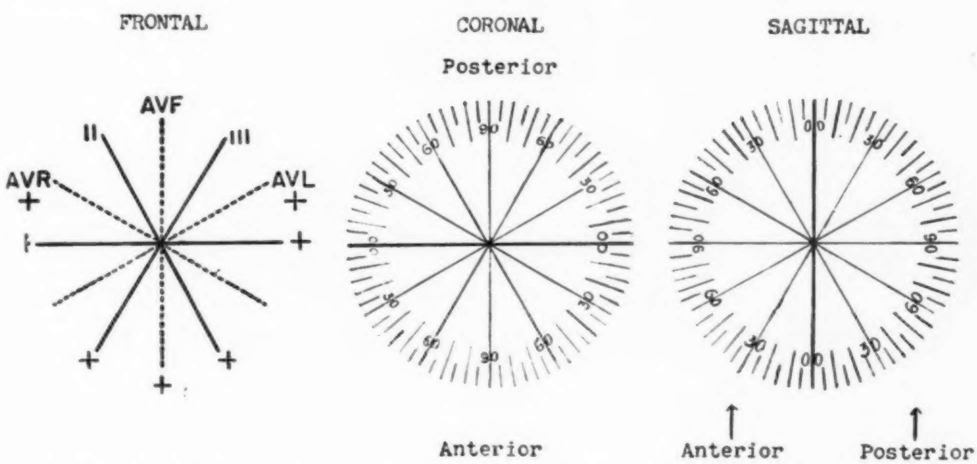

Fig. 2.—The form used to record the position of the vectors. (The term "coronal," applied to the transverse body plane, has been replaced by the more generally accepted and understood term, "horizontal.")

Briefly, the model is used in this fashion: The frontal plane projection of the mean QRS vector is determined by any one of several methods. Inasmuch as it is also the mean electrical axis of Einthoven, it can be determined according to methods for determining this well-known vector. However, in practice we use a projection system devised by Grant[3] which takes advantage of the fact that any limb lead which has the highest amplitude will be one which roughly parallels the mean vector. Likewise if in any of the six extremity leads there is found one in which the complex is isopotential (approximately as much positive deviation as negative), it is certain that the vector is directed at right angles to the axis of that lead. With practice it is soon possible to determine quickly the direction of the vector in the frontal plane, within an error which is rarely over 5 degrees. Having determined the direction of the frontal vector, this is recorded in the hexaxial system, and the pointer in the model (which represents the vector) is moved to that position. To determine the spatial characteristics of the vector

we then take advantage of another well-established electrical principle. If we represent an electrical field by a dipole in a volume conductor there will be lines of force about the positive and negative poles of the dipole. This electrical field may be presented by a vector running through the dipole, from sink (negative) to source (positive). (We are here not concerned with lines of flow, which would be represented by a vector in the opposite direction.) At right angles to any such vector, equidistant between source and sink, there will be a plane of isopotentiality, neither negative nor positive. In electrocardiography we base our present theories on the dipole principle, and assume that the electrical activity

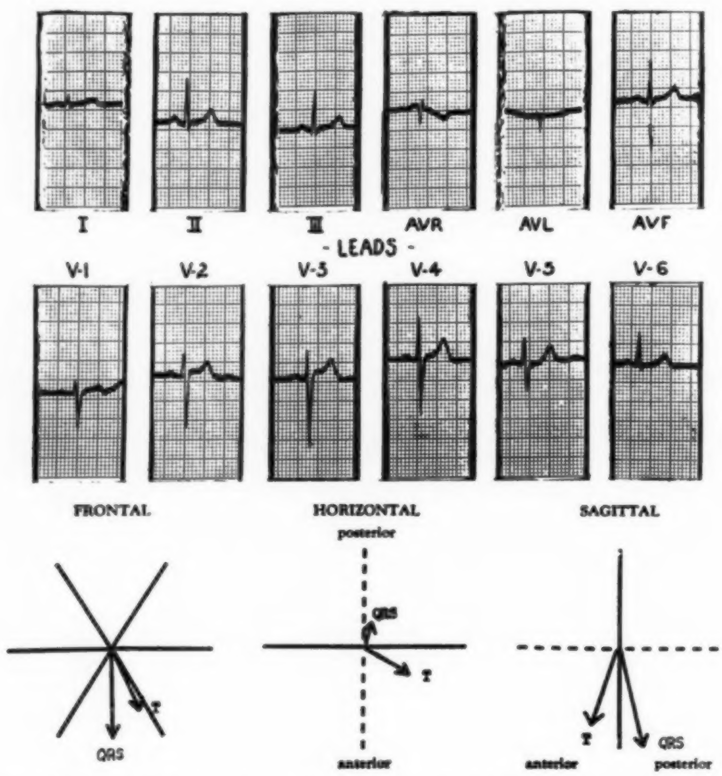

Fig. 3.—The QRS and T Vectors in an electrically vertical heart. (In this, and in all subsequent illustrations, most of the reference lines shown in Fig. 2 have been removed for clarity of presentation.)

of the heart is made up of an infinite number of such dipoles. The summation of all such dipoles may likewise be assumed to act like a single dipole, and the vector derived therefrom is the mean spatial vector. If this is true there should be a plane around the body analogous to the above-mentioned isopotential plane. Grant has been able to demonstrate such a plane in all cases. Inasmuch as the body is not a perfect cylinder, such a plane may not be mathematically exact, but the variations from the predicted findings are rarely of importance. This plane may well be called the transitional zone, a term with which we are already familiar in interpreting precordial leads. It is not within the scope of this paper

to go into theoretic considerations regarding this transitional zone, which has heretofore been generally assumed to lie over the septum. It has been adequately proved that this concept is frequently in error, for reasons which the reader may determine from Grant's publications listed above. At any rate, this transitional zone lies at right angles to the mean spatial vector. Therefore, we search the precordial leads for a transitional complex, or for the space between complexes where transition has occurred. Having determined this point we then rotate the transitional plane of the model until it intersects the point on the chest where the transitional complex was found. The mean vector is kept in the frontal plane

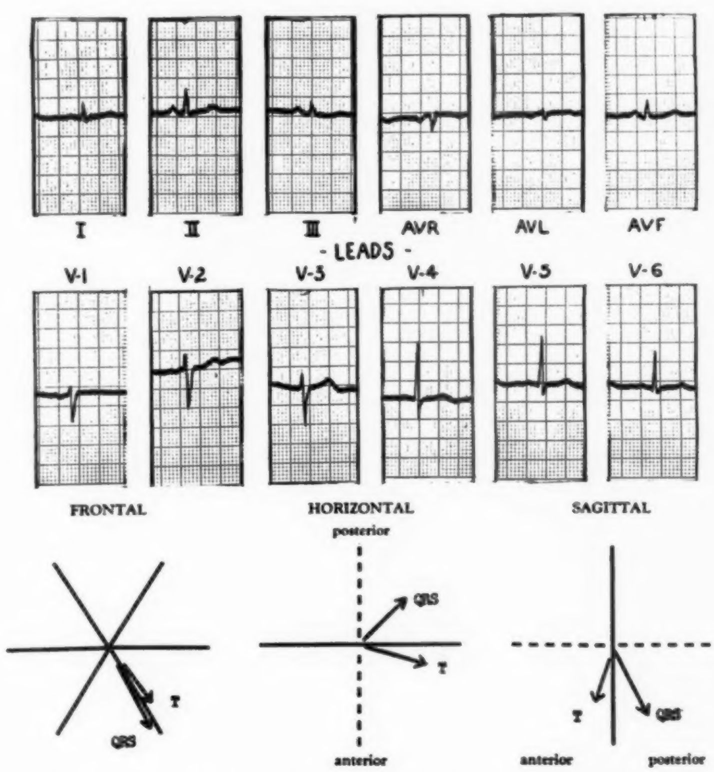

Fig. 4.—The QRS and T Vectors in an electrically semivertical heart.

projection previously determined by sighting through the model to the hexaxial system engraved behind the chest. When the mean vector is in this position, and the transitional plane intersects the chest correctly, the horizontal and sagittal directions of the vector can be easily determined visually, and recorded on the chart shown in Fig. 2. To the uninitiated this may sound complex, but it is with practice a very simple procedure, and the experienced observer has no difficulty in approximating the spatial vector by simple inspection, without using the model. As is well known, the transitional zone for the QRS vector is almost always found in the usual six unipolar precordial leads.

The T vector is determined in the same manner, although the transitional zone is frequently farther to the right, and additional right sided leads may be needed.

In this paper we are concerned only with the normal QRS and T vectors, but the same system may be used to determine the P vector, the S-T vector, or the vector for any portion of the cycle. Reasonably accurate loops, or vectorcardiograms, can be drawn by calculating a number of separate vectors at intervals through the QRS cycle, drawing these vectors on the scales, and connecting the tips of the vectors with a continuous line.

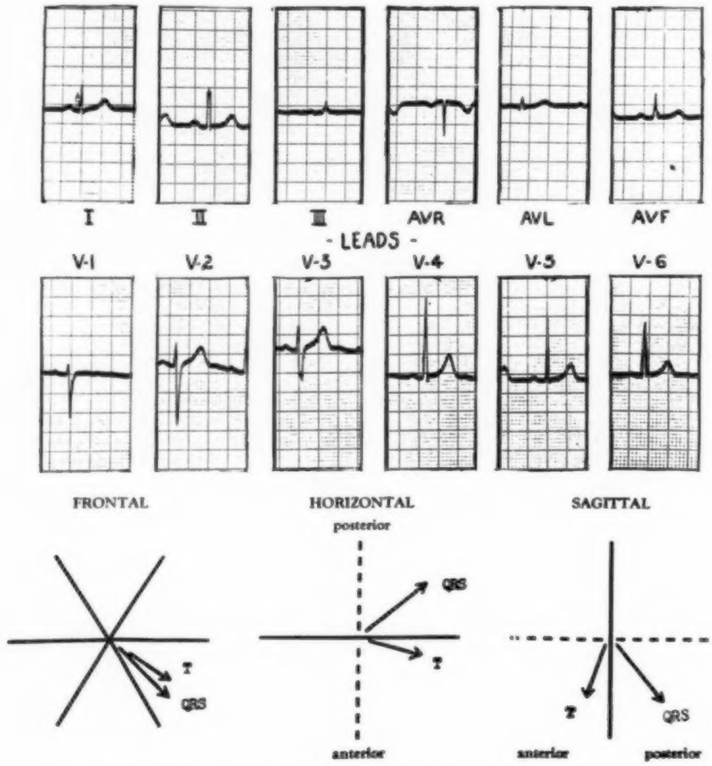

Fig. 5.—The QRS and T Vectors in an electrically intermediate heart.

MATERIAL

Inasmuch as we are here dealing with a new method for which there are no established standards of normality, it has been our first effort to determine such standards. It is obvious that this will require a great deal of time, and the analysis of large numbers of electrocardiograms, but in order that there might be a starting point for further study we selected a group of apparently normal individuals for vector analysis. Each of these people had a complete physical examination, chest roentgenogram, cardiac fluoroscopy, twelve lead electrocardiogram, and a number of blood and urine studies. No patient was used who had any evidence of cardiac pathology, as determined from the above studies

plus a careful history, and special studies such as venous pressure, circulation time, etc. Because it is well known that body build and chest configuration influence the appearance of the electrocardiogram, we have made an analysis of

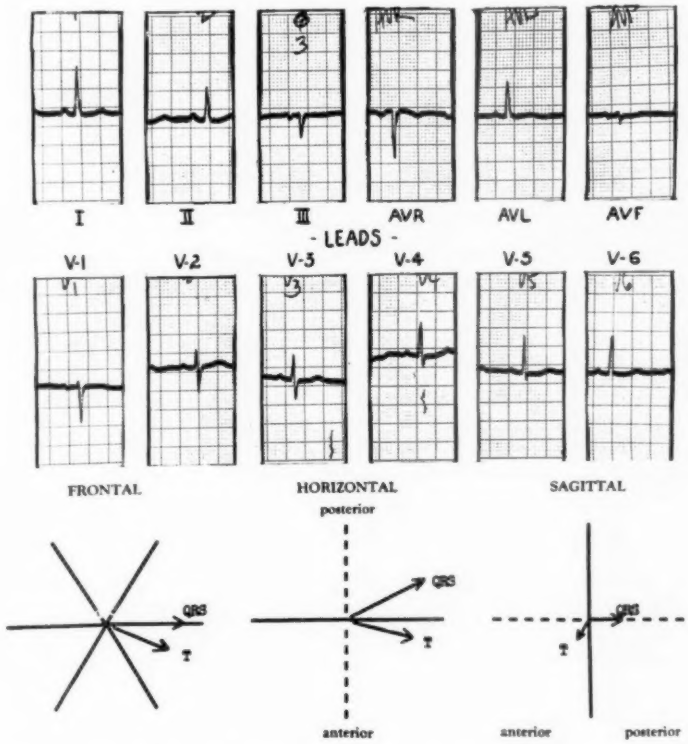

Fig. 6.—The QRS and T Vectors in an electrically semihorizontal heart.

such factors in these patients, and this will be reported at a later date. We selected fifty men and fifty women from a group of over 2,500 individuals on whom twelve lead electrocardiograms had been done. The only criteria for inclusion were that they had no evidence of cardiac pathology in any form; that they had no disease of the lungs, chest, diaphragm, or mediastinum which would affect cardiac position, and that they were in the adult age group. The age limits were 17 to 71, the average age of the women was 46 years, of the men was 43 years.

In this paper we are interested only in illustrating the various electrical positions of the mean spatial QRS and T vectors. We will make no effort to correlate weight, body build, age, or other factors. Neither are we especially interested in the QRS-T angle, although it was normal in all of these subjects. We have merely selected a number of illustrative electrocardiograms, with the appropriate vector analysis, so that the interested reader may become familiar with the appearance of the normal. Because the electrical positions described originally by Wilson and associates[8] are familiar to almost everyone, we have chosen to present these examples according to that classification. This also serves as a good demonstration of one advantage of Grant's method. For instance, in

Fig. 3, the experienced electrocardiographer can look at the electrocardiogram and determine by the configuration of the unipolar extremity leads that we are probably dealing with an electrically vertical heart. He has learned by experience and study that a negative deflection in aV_L and a positive one in aV_F means a vertical heart, if the precordial leads are normal. But the same information is readily apparent by looking at the vector analysis. The mean spatial QRS vector is pointing almost straight down and, therefore, this is a vertical heart. No memory pattern is needed. Likewise, in Fig. 7, the electrocardiogram is classical for an electrically horizontal heart, but one has only to look at the vector pattern to see that it is such a heart. (Correlation and lack of correlation between electrical and anatomic positions of the heart will be the subject of a subsequent paper. We are interested in this presentation only in demonstrating electrical position.)

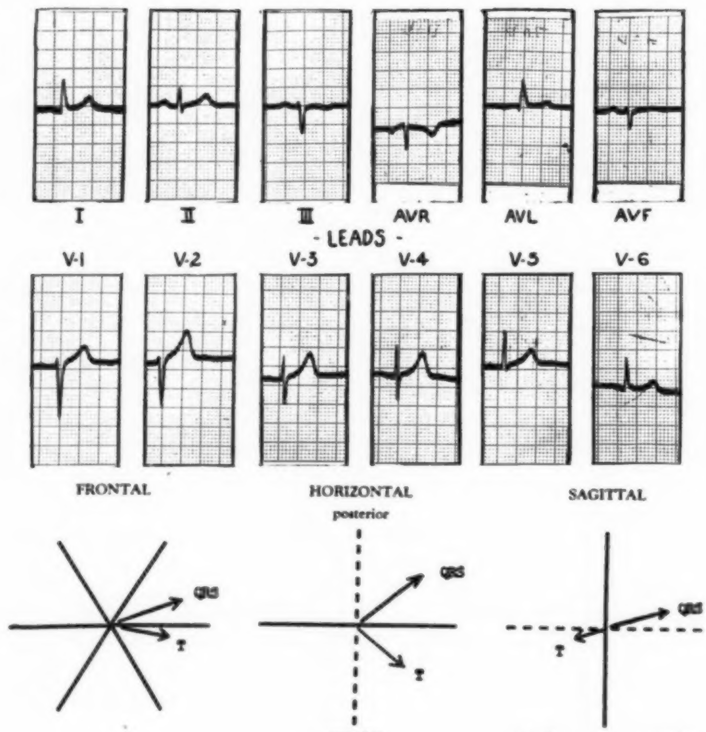

Fig. 7.—The QRS and T Vectors in an electrically horizontal heart.

THE VECTORS AND ELECTRICAL POSITION

In the vertical or semivertical heart, the normal QRS and T vectors are directed in a caudad direction. Because of this the principal projections of the vectors are in the frontal and sagittal planes. The horizontal projections are small and quite variable, but as we shift from the truly vertical to the semivertical the vectors are directed more to the left, and the projections in the horizontal plane become larger. In Fig. 3 we have shown a classic electrically vertical heart,

in Fig. 4 a semivertical one. In Fig. 8, a number of such vector analyses have been included to show the transition which occurs.

We have shown only one intermediate heart with electrocardiogram and vector analysis, (Fig. 5), in Fig. 9 we have shown several such vector analyses, with the mean QRS vector ranging from nearly semivertical to nearly semi-

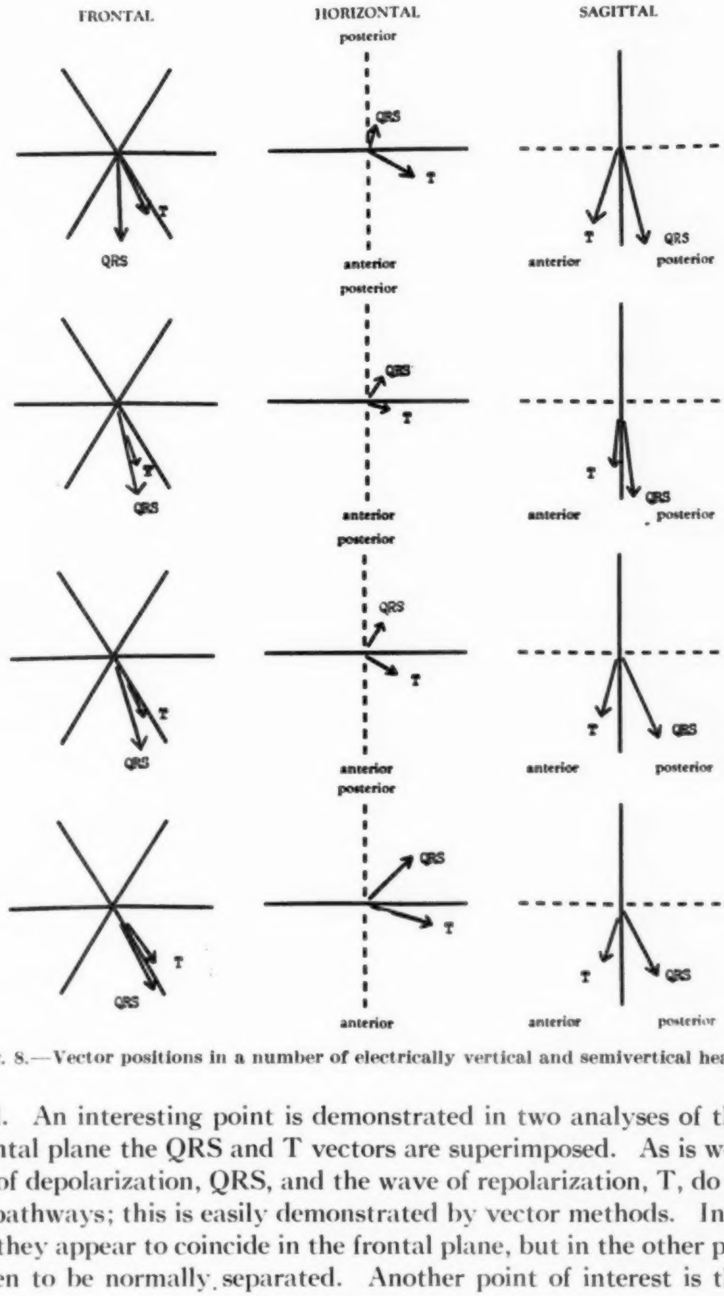

Fig. 8.—Vector positions in a number of electrically vertical and semivertical hearts.

horizontal. An interesting point is demonstrated in two analyses of this group; in the frontal plane the QRS and T vectors are superimposed. As is well known, the wave of depolarization, QRS, and the wave of repolarization, T, do not follow identical pathways; this is easily demonstrated by vector methods. In these two instances they appear to coincide in the frontal plane, but in the other planes they can be seen to be normally separated. Another point of interest is that as the

vectors approach the horizontal they are pointing more or less directly to the left, or at right angles to the sagittal plane. Therefore, the deflections on the latter plane are of decreasing magnitude. This is a situation comparable to the projections on the horizontal plane in the vertical heart.

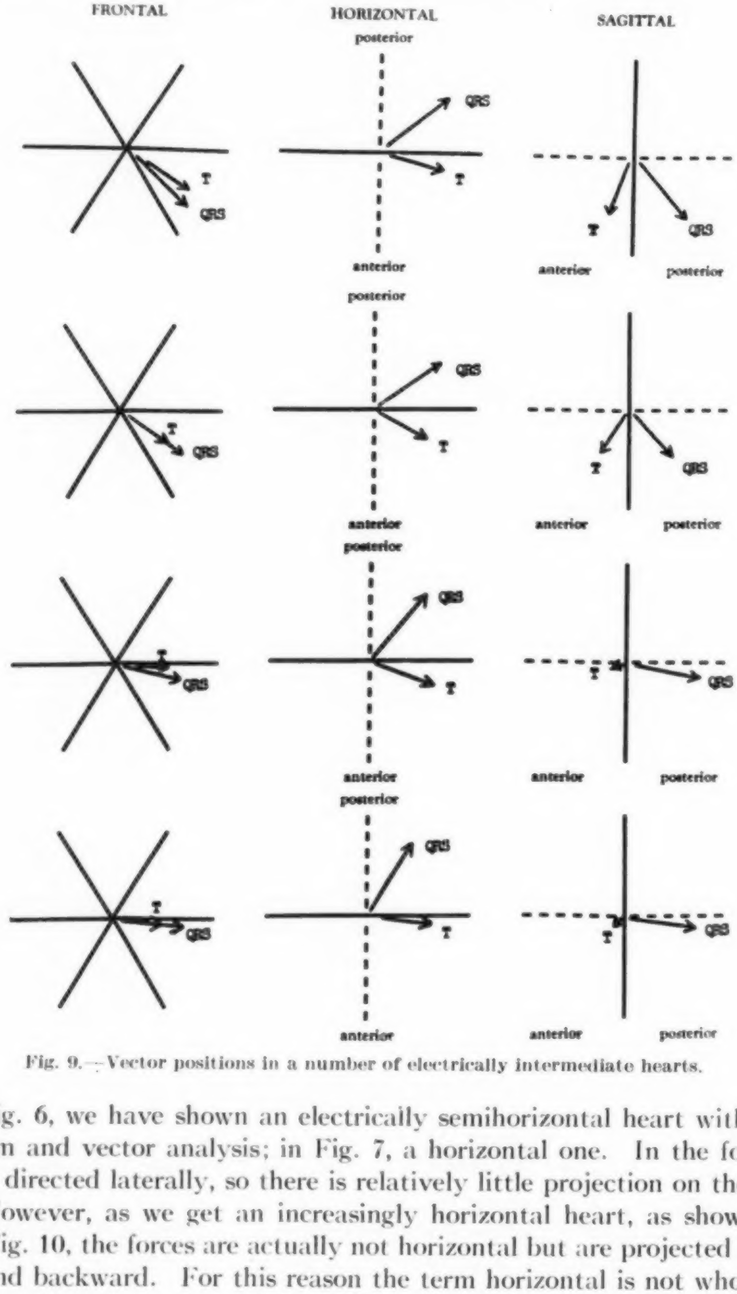

Fig. 9.—Vector positions in a number of electrically intermediate hearts.

In Fig. 6, we have shown an electrically semihorizontal heart with electrocardiogram and vector analysis; in Fig. 7, a horizontal one. In the former the forces are directed laterally, so there is relatively little projection on the sagittal plane. However, as we get an increasingly horizontal heart, as shown in the series in Fig. 10, the forces are actually not horizontal but are projected laterally, upward and backward. For this reason the term horizontal is not wholly accurate. The only truly horizontal heart in an electrical sense is the one which we call semihorizontal, Fig. 6.

It can be seen from this brief presentation that the effort to catalogue electrocardiograms according to electrical position is only partially correct. Instead of five positions there are an infinite number from the most horizontal (which we have shown is not truly horizontal) to the most vertical. And in this group we were concerned only with normal individuals. When we consider the extremes of

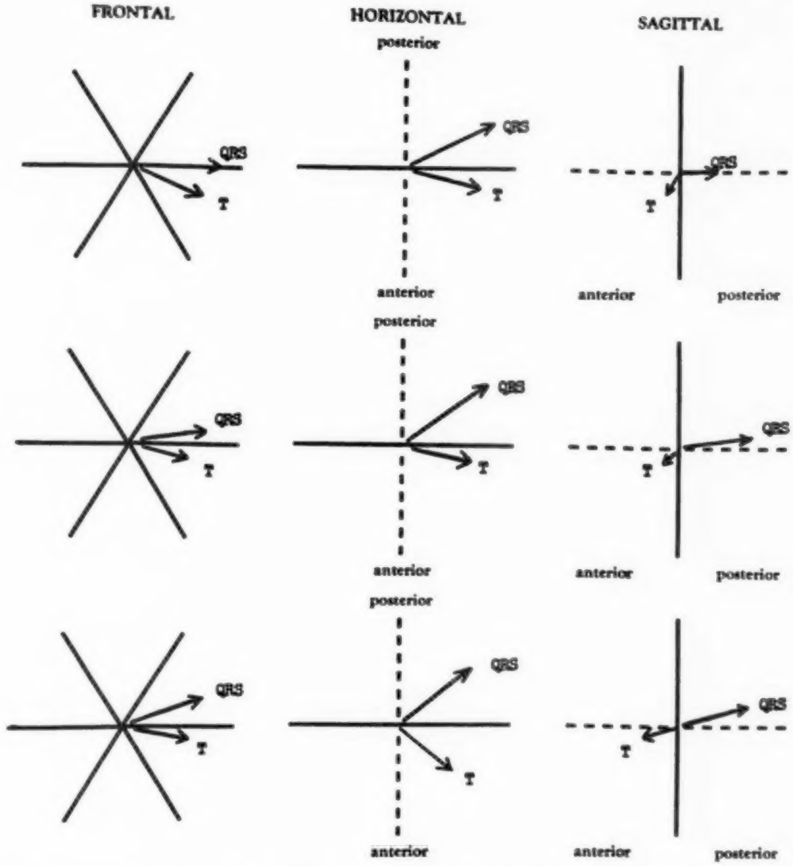

Fig. 10.—Vector positions in a number of electrically semihorizontal and horizontal hearts.

the abnormal individuals, such as the severe hypertensive type, or the congenital cardiac subjects with massive right heart hypertrophy and right axis deviation, we find vectors far beyond the ranges we have shown at this time. It appears much simpler and more sound to consider the electrical field of the heart from the vector point of view, and to forego memorizing patterns of position.

SUMMARY AND CONCLUSIONS

1. The mean spatial vector method developed by Grant has been briefly reviewed, with emphasis at this time only on direction of the QRS and T vectors in normal individuals.

2. To facilitate this presentation, these normal cardiograms were classified according to the electrical positions described by Wilson. We have shown that the mean spatial vector method is a more satisfactory way to demonstrate electrical position from the visual point of view. It is not necessary to memorize patterns of deflection to know the position of the electrical field of the heart.

3. In this paper no effort was made to correlate body build and electrical position, nor was any attention devoted to sex variations, or to statistical analysis of the group as a whole. It was our sole intention at this time to demonstrate a number of normal QRS and T vectors, derived and inscribed by our method, so that this might serve as a basis for further work with normal and abnormal subjects.

REFERENCES

1. Grant, R. P.: An Approach to the Spatial Electrocardiogram, Am. Heart J. **39**:17, 1950.
2. Grant, R. P.: The Relationship of Unipolar Chest Leads to the Electrical Field of the Heart, Circulation **1**:878, 1950.
3. Grant, R. P.: Spatial Vector Electrocardiography. A Method for Calculating the Spatial Electrical Vectors of the Heart From the Conventional Leads, Circulation **2**:676, 1950.
4. Grant, R. P., Estes, E. H., and Doyle, J. T.: Spatial Vector Electrocardiography. The Clinical Characteristics of S-T and T Vectors, Circulation **3**:182, 1951.
5. Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Co.
6. Urschel, D. L., and Abbey, D. C.: Modification of a Vector Model to Provide Accurate Recording of Mean Vector Positions in Three Planes of Space, Am. Heart J. **44**:3, 1952.
7. Robertson, D.: On Consistency in Convention of Sign in Electrocardiography and Vectorcardiography, Am. Heart J. **42**:912, 1951.
8. Wilson, F. N., Johnston, F. D., Cotrim, N., and Rosenbaum, F. F.: Relations Between the Potential Variations of the Ventricular Surfaces and the Form of the Ventricular Electrocardiogram in Leads from the Precordium and the Extremities, Tr. A. Am. Phys. **56**:258, 1941.

A SIMPLE DIAGRAM TO ILLUSTRATE THE RELATIONSHIPS BETWEEN EXTREMITY LEADS

LOUIS A. SOLOFF, M.D. AND JACOB ZATUCHNI, A.B., M.S., M.D.

PHILADELPHIA, PA.

IT HAS been shown previously that there are only two independent equations for the three Einthoven leads, the three Wilson extremity leads, and the three augmented Wilson extremity leads.[1] Just as the algebraic sum of the Einthoven leads is zero, so is the algebraic sum of either of the other two.

The diagrams in Fig. 1 clearly demonstrate these relationships. Each Einthoven lead occupies one side of a triangle, so that the three traverse the triangle once, starting and ending at the same point. Each augmented Wilson extremity lead occupies two sides of a triangle; the three traverse the triangle twice, starting and ending at the same point. Each Wilson extremity lead traverses the entire triangle once, so that the three traverse the triangle three times, starting and ending at the same point.

If going around the triangle once (the Einthoven leads) equals zero (Kirchhoff's law), passing around the triangle twice equals twice zero, passing three times equals three times zero, passing n times equals n times zero or zero. Therefore, the algebraic sum of each set of leads is zero.

The relationship of the augmented Wilson extremity leads (aV) to the Wilson extremity leads (V) is shown by the following equation:

$$V = a - \frac{a + b + c}{3}$$

$$V = \frac{3a - a - b - c}{3}$$

$$\text{or, } V = \frac{2a - b - c}{3}$$

$$aV = a - \frac{b + c}{2}$$

$$\text{or, } aV = \frac{2a - b - c}{2}$$

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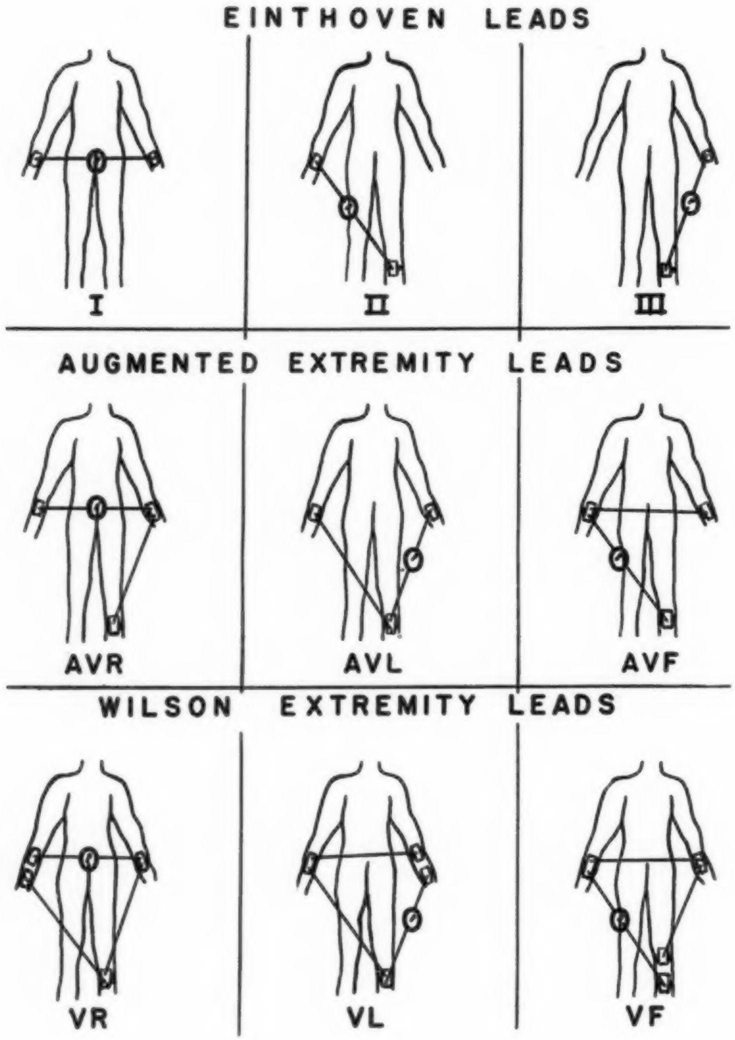

Fig. 1.—The circuit of the various extremity leads. The algebraic sum of the electromotive forces of any set of circuits, starting and ending at the same point, is zero. In the set of Einthoven leads the circuit traverses the triangle once, in the augmented Wilson extremity leads twice, and in the Wilson extremity leads three times.

$$\text{Dividing,}\quad \frac{aV}{V} = \frac{\dfrac{2a - b - c}{2}}{\dfrac{2a - b - c}{3}} = \frac{3}{2}$$

$$\therefore aV = 1.5V$$

Therefore, by construction the algebraic sum of each set of leads is zero and the augmented Wilson extremity leads are 50 per cent greater than the Wilson extremity leads. These relationships are purely mathematical and have no bearing on the nature of the body as an electrical conductor.

If the reader should take electrocardiograms using the circuits we have shown in the diagrams, he will observe that there are minor differences between the electrocardiograms so taken and those taken with the conventional method with the conventional instruments. The reason for the differences lies in the fact that no allowance is made in our circuit for unequal skin resistances. This is the reason that Wilson interposed high resistances between the electrodes and the reason for having the central terminal away from the skin.

REFERENCES

1. Soloff, L. A.: The Relationship of Lead II to Lead I in Posterior Infarction and its Bearing on the Configuration of Lead aVF, Am. Heart J. **40**:839, 1950.

THE Q-T INTERVAL IN MYOCARDIAL INFARCTION AND LEFT VENTRICULAR HYPERTROPHY

STEPHEN R. ELEK, M.D., ALFRED S. SILVER, M.D., JEROME N. TOBER, M.D., AND GEORGE C. GRIFFITH, M.D.

LOS ANGELES, CALIF.

THE REPORTS of Taran and Szilagyi[1] that prolongation of the Q-T interval sharply differentiated active from inactive rheumatic carditis in children, and of Bellet and Dyer[2] that prolongation of the Q-T interval was a sensitive indicator of impending hypopotassemic collapse during treatment of diabetic coma and in other important clinical situations, have stimulated the interest of clinicians in the Q-T interval or electrical systole.

All observers agree that the Q-T interval can be interpreted only after correction for its inherent proportionality to cycle length. Many agree that sex and age corrections must also be made. Numerous suggestions have been made as to the nature of this correction. The most important have been by Bazett,[3] who stated that the Q-T interval varies as the square root of the cycle length; Adams,[4] that the relationship is best expressed as an arithmetic regression, and Ashman and Hull,[5] that the relationship is logarithmic. In a study of 1,000 normal men and women, Ashman and Hull[6] found that the formula $Q - T = K [10(c+k)]$ best fits their data. In this formula, C is cycle length and K is 0.07. In the group 45 years or older, the mean K value for men is 0.380 and for women 0.390, while the maximum normal K values are stated to be 0.410 for men and 0.420 for women.

Despite the large size of Ashman's control series, exceeding other normal series in the literature and confirming Bazett's earlier finding of a significantly longer Q-T interval for women, most workers have utilized Bazett's formula, ignoring the sex difference, some rounding off the constant to 0.40 as a mean for all cases.[7] The ground usually given for this action is "simplicity" yet most of these same workers rely on nomograms or graphic curves for solving the "simple" formula,[8,9] which methods are just as simply applied to the logarithmic formula.

Two general approaches have been employed in the analysis and comparison of Q-T intervals. With the first method the expected ("predicted" or "calculated") Q-T interval is derived by formula or by graph from the observed cycle length and compared with the observed Q-T interval, the comparison holding only for the one cycle length. The comparison has been expressed as a Q-T ratio.[8]

The second method of comparison reduces all Q-T intervals to a value independent of cycle length, thereby affording a simpler and more flexible analysis.

From the Department of Medicine (Cardiology), School of Medicine, University of Southern California and the Los Angeles County Hospital, Los Angeles, Calif.

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This is accomplished by substituting the observed Q-T interval and observed cycle length into the desired formula and solving for the K value which thereby comes to signify Q-T interval per unit cycle length. Taran and Szilagyi[1] introduced the symbol QTc (corrected Q-T interval) for the K value. K values are not interchangeable between formulas and must not be crosscompared. For this reason and because of the numerous symbols such as QTcal, QTpred, and QT ratio, we prefer to retain the symbol "K" and specifically designate from which formula the K value is derived. The confusion of formulas and symbols has already resulted in highly questionable conclusions. In commenting on Taran's conclusions concerning the Q-T interval in rheumatic fever, Craige and associates[10] in an important paper pointed out that Taran used a K value of 0.405 derived from Bazett's formula as the upper limit of normal. However, this K value of 0.405 is derived from Ashman's formula representing the mean Q-T interval in a series of 700 individuals with heart disease predominantly of hypertensive-arteriosclerotic etiology. Subsequent papers by Pokress and Goldberger[7] and Craige and associates[10] corroborate a widespread clinical impression that rheumatic activity is not so universally indicated by Q-T interval prolongation beyond a Bazett K value level of 0.405 as the original analysis claimed. Summaries of the factors affecting the Q-T interval have been published.

That the Q-T interval should be in part a function of heart size seems a reasonable hypothesis, providing that the rate of depolarization and repolarization remains fixed in the face of increasing fiber length and/or width. This concept is reinforced by White and associates'[11] finding of a prolonged Q-T interval in the elephant. However, in human beings little increase in Q-T interval occurs from infancy to maturity.[6,12] In a previous study,[13] analyzing twenty-six cases of cardiac enlargement, eleven without and fifteen with congestive failure, it was concluded that the Q-T interval is relatively prolonged with cardiac enlargement and more so with congestive failure, becoming shorter upon recovery from failure. Re-evaluation of this data, however, reveals a mean K value (Ashman) of only 0.405 for the eleven cases without failure; this figure rests between Ashman's mean 0.38 and maximum 0.41 normal. Dock[14] found the Q-T interval prolonged in only one-third of the subjects with cardiac failure.

The prolongation of Q-T interval in myocardial infarction has been noted by several authors.[6,15] We studied this subject systematically in 1946.[16] Recently, Krasnoff[17] reported definite prolongation with myocardial infarction in 496 subjects and in a smaller group noted progressive shortening towards normal in serial studies during the first six weeks following infarction. However, in any series of myocardial infarction, left ventricular hypertrophy is very likely present although its influence on the Q-T prolongation was not studied by Krasnoff. The present study was undertaken to clarify the effect of myocardial infarction and left ventricular hypertrophy on the Q-T interval.

METHOD

Only electrocardiograms with sharply recognizable T waves in at least one lead were included in this study. Lead II was usually used. The average value

of at least five consecutive complexes were taken. Marked arrhythmia, digitalis effect, or bundle branch block were excluded. Measurements of both Q-T intervals and cycle lengths were limited to the nearest 0.01 second since it was felt that despite magnification techniques the almost invariably gradual return of the terminal limb of the T waves to the isoelectric line constituted a limiting factor to the accuracy of the Q-T interval measurement and to subsequent computations.

Our original series of left ventricular hypertrophy and myocardial infarction was obtained in 1946.[16] Since that time additional series were obtained for comparison and verification because of the inclusion of unipolar limb leads and a change from the use of CF to V leads, as well as improved diagnostic criteria.

All cases of myocardial infarction had characteristic electrocardiographic changes as well as typical clinical histories and confirmatory laboratory data. They were taken chronologically, selection being limited to exclusion of unsatisfactory or unconvincing tracings or case histories.

The 1946 series of left ventricular hypertrophy was selected on the basis of radiographic confirmation[18] of ventricular enlargement and S-T segment and T-wave changes considered characteristic of left ventricular strain and hypertrophy.

The 1951 series of left ventricular hypertrophy was selected to include only cases demonstrating, by radiography, enlargement and showing a classical well-advanced pattern of "left ventricular hypertrophy" as noted by Wilson and his associates[19] and evaluated by Sokolow and Lyon's[20] criteria. By comparison with the series of the latter authors using eleven different criteria of abnormality as suggested by their paper, our series showed a higher per cent of abnormality for each criterion.

Ashman's mean normal K value of 0.380 for men and women, respectively, with comparable maximum normal K values of 0.410 and 0.420 were accepted on the basis of his extremely large normal series. Standard statistical methods were applied to the findings.[21]

RESULTS AND DISCUSSION

Table I summarizes the findings in eighty-six cases of acute myocardial infarction and 140 cases of left ventricular "strain" and hypertrophy. The cases have been considered according to sex, with the group collected in 1951 separated from the cases measured five years earlier for reasons already mentioned. Mean K values for all infarction groups are definitely and significantly prolonged beyond Ashman's upper limit of normal. On the other hand mean K values for all the hypertrophy groups lie well below the upper limit of normal and all but one lie at or below the mean normal values of Ashman.

Analysis of the sex difference fails to reveal any consistency in our series since probability values indicate no significant sex difference in the 1951 infarction group or the 1946 hypertrophy group. In the remaining groups the sex difference is greater but falls so close to the border line that no importance can be attached to it.

Fig. 1 is a semilogarithmic graph plotting K values against the logarithm of cycle lengths for several clinical entities as indicated in the legend. By this means Ashman's curve is transformed into a straight line relationship which permits rapid comparison of observed and predicted Q-T intervals whenever such comparisons are made. In addition, the semilogarithmic graph may be used for rapid determination of K value in this manner: from the point of intersection of an observed Q-T interval and an observed cycle length, proceed along the normal slope (parallel to the normal line) to unit cycle length (that is, 1.00 + 0.07). The Q-T interval (abscissa) intersecting this slope at unit cycle length is the approximate K value. The introduction of a semilogarithmic plot provides only a convenient means of comparing a given Q-T interval and a cycle length with an accepted standard of normal. As pointed out above, for analytical purposes the observed Q-T interval should be reduced to its K value by computation in order to give it a significance devoid of dependence upon cycle length.

TABLE I.

LESION	SEX	AGE RANGE	NO. OF CASES	NO. OF ECG'S	OBSERVED Q-T MEAN ± S.E.M.*	K (ASHMAN) MEAN ± S.E.M.*	P VALUE. K MALE TO FEMALE†
Acute infarction, 1946 series	M F	36 to 68 52 to 74	40 16	140 55	0.389 ± 0.004 0.399 ± 0.008	0.413 ± 0.003 0.427 ± 0.006	<0.05
Acute infarction, 1951 series	M F	40 to 75 51 to 72	21 9	21 9	0.396 ± 0.009 0.398 ± 0.018	0.425 ± 0.006 0.433 ± 0.013	>0.5
Left ventricular hypertrophy, 1946 series	M F	40 to 82 17 to 76	31 31	40 52	0.361 ± 0.003 0.359 ± 0.003	0.384 ± 0.004 0.382 ± 0.002	>0.6
Left ventricular hypertrophy, 1951 series	M F	30 to 78 42 to 72	27 31	27 31	0.387 ± 0.008 0.363 ± 0.007	0.406 ± 0.006 0.390 ± 0.005	<0.05

*S.E.M., Standard error of the mean = $\sqrt{\frac{\Sigma\Delta^2}{n\ (n-1)}}$

†P value, Probability value[21]; a P value of less than 0.05 indicates a significant difference between the values compared.

It is obvious from mere inspection of K values that sufficient scatter is present in all groups to prevent clinical inference being drawn from any given Q-T interval. For example, in the 1951 group of female hypertrophy cases with a mean K value of 0.390 there is a spread of K values from 0.34 to 0.44 with five cases longer than 0.41 and six cases shorter than 0.38. This does not necessarily detract from the value of serial observation of Q-T intervals in a single case.

In the 1946 series of acute infarctions there were forty-seven cases available with serial tracings revealing definite evolution of the infarction pattern; electrocardiographic follow-up averaged 18.2 days with a maximum of sixty-seven days. The mean change in K value in the entire group was only 0.017 second, which is insignificant. In the eleven cases with a mean follow-up of 34.8 days the mean change of K value was only 0.011 second which is also insignificant.

The findings in Table I establish the absence of Q-T prolongation in left ventricular hypertrophy, especially since our cases included only classical and

advanced electrocardiographic patterns and uniformly revealed mean K values remarkably close to Ashman's normals (both mean and upper limit).

Our data corroborate previous observations regarding a prolonged Q-T interval in acute myocardial infarction but do not support the finding[16] of a gradual reversion toward normal during the first six weeks after infarction. However, the number of cases in our series followed for six weeks was small and further data are needed.

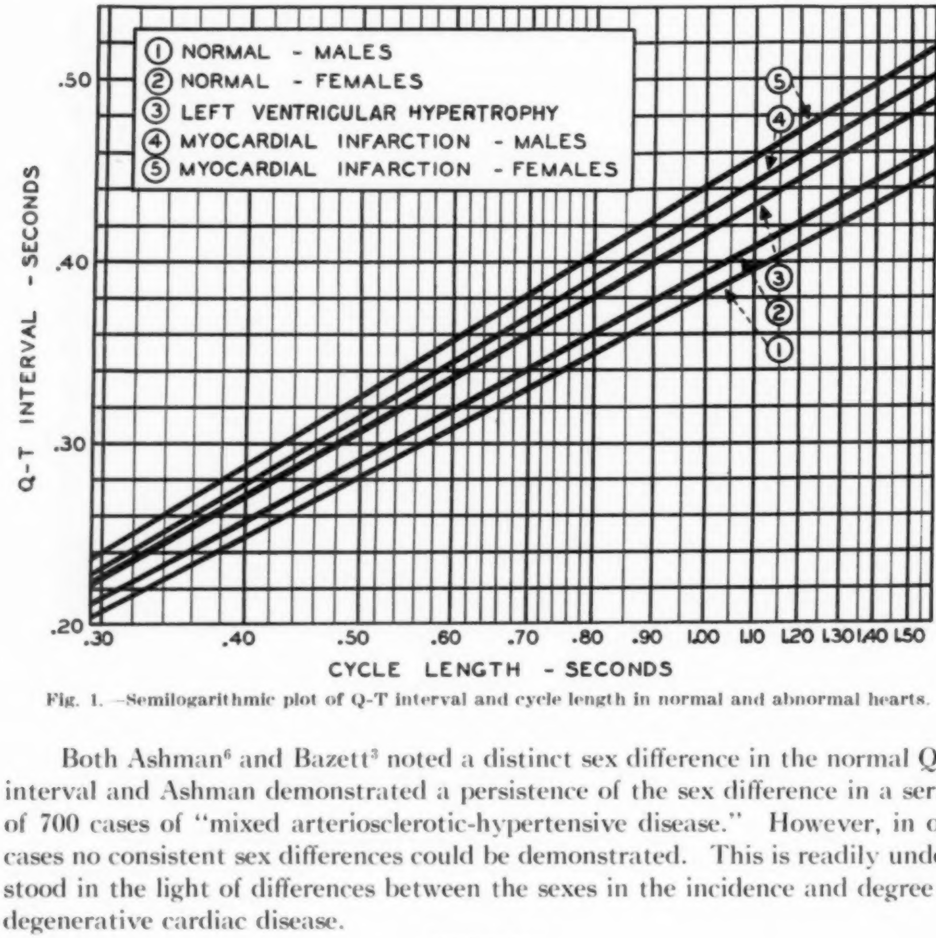

Fig. 1.—Semilogarithmic plot of Q-T interval and cycle length in normal and abnormal hearts.

Both Ashman[6] and Bazett[3] noted a distinct sex difference in the normal Q-T interval and Ashman demonstrated a persistence of the sex difference in a series of 700 cases of "mixed arteriosclerotic-hypertensive disease." However, in our cases no consistent sex differences could be demonstrated. This is readily understood in the light of differences between the sexes in the incidence and degree of degenerative cardiac disease.

SUMMARY

1. By the use of semilogarithmic plotting, the Q-T formula of Ashman is simplified and reduced to a straight line.

2. In 120 cases of left ventricular hypertrophy, no significant prolongation of the Q-T interval was found.

3. In eighty-six cases of acute myocardial infarction, the Q-T interval was significantly prolonged. The data did not confirm a previous report that the prolonged Q-T interval is gradually reduced during the first few weeks after myocardial infarction.

REFERENCES

1. Taran, L. M., and Szilagyi, N.: The Duration of Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children, Am. Heart J. **33**:14, 1947.
2. Bellet, S., and Dyer, W. W.: The Electrocardiogram During and After Emergence From Diebetic Coma, Am. Heart J. **13**:72, 1937.
3. Bazett, H. C.: An Analysis of the Time Relations of Electrocardiograms, Heart **7**:353, 1920.
4. Adams, Wright: The Normal Duration of the Electrocardiographic Ventricular Complex, J. Clin. Investigation **15**:335, 1936.
5. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Company.
6. Ashman, Richard: The Normal Duration of the Q-T Interval, Am. Heart J. **23**:522, 1942.
7. Pokress, M. J., and Goldberger, E.: A Study of the Q-T Interval in Rheumatic Fever, Am. Heart J. **38**:423, 1949.
8. Goldberger, E.: A Simple Method of Determining Abnormalities of the Q-T Interval, Am. Heart J. **36**:141, 1948.
9. Kissin, M., Schwarzschild, M. M., and Bakst, Hyman: A Nomogram for Rate Correction of the Q-T Interval in the Electrocardiogram, Am. Heart J. **35**:990, 1948.
10. Craige, E., Alimurung, M. M., Bland, E. F., and Massel, B. F.: The Q-T Interval in Rheumatic Fever, Circulation **1**:1338, 1950.
11. White, P. D., Jenks, J. L., Jr., and Benedict, F. G.: The Electrocardiogram of the Elephant, Am. Heart J. **16**:744, 1938.
12. Alimurung, M. M., Joseph, L. G., Craige, E., and Massel, B. F.: The Q-T Interval in Normal Infants and Children, Circulation **1**:329, 1950.
13. Phang, S. S., and White, P. D.: The Duration of Ventricular Systole as Measured by the Q-T Interval of the Electrocardiogram, With Special Reference to Cardiac Enlargement With and Without Congestive Failure, Am. Heart J. **26**:108, 1943.
14. Dock, William: Duration of Electrical Systole as an Index of Myocardial Deficiency, Am. Heart J. **6**:590, 1931.
15. Katz, L. N.: Factors Modifying the Duration of Ventricular Systole, J. Lab. & Clin. Med. **6**:291, 1921.
16. Elek, S. R., and Tober, J. N.: The Q-T Interval in Myocardial Infarction; Read Before the Western Society for Clinical Research, Nov. 2, 1946, San Francisco, Calif.
17. Krasnoff, S. O.: The Duration of the Q-T Interval in Myocardial Infarction, Am. Heart J. **39**:523, 1950.
18. Ungerleider, H. E., and Gubner, R.: Evaluation of Heart Size Measurements, Am. Heart J. **24**:494, 1942.
19. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E, Hecht, H., Cotrim, N., DeOlevera, R. M., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.
20. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **37**:161, 1949.
21. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1935, Oliver & Boyd, Ltd.

ANATOMIC AND ELECTROCARDIOGRAPHIC CORRELATION IN COMBINED VENTRICULAR HYPERTROPHY

Mortimer B. Lipsett, M.D.,* and Willard J. Zinn, M.D.**

Los Angeles, Calif.

Although academically and clinically important, the diagnosis of combined ventricular hypertrophy of the heart by electrocardiographic criteria is difficult. There have been relatively few published collections of electrocardiographic tracings demonstrating this pattern. The present study is an analysis of the electrocardiographic patterns in seventy-three necropsied cases with combined ventricular hypertrophy.

In 1943 Langendorf and associates[1] reviewed their files for electrocardiographic patterns of combined ventricular strain. Their diagnosis at that time utilized combinations of axis deviation and ST-T changes. With the introduction of the unipolar leads, many previous concepts were found to be erroneous, and this group subsequently[2] analyzed a larger series containing unipolar lead tracings. However, only two of their cases were confirmed by autopsy. They noted that electrocardiographic evidence of combined ventricular hypertrophy depended on the electrical position and rotation of the heart. Precordial and standard lead ST-T and T-wave patterns contributed to the diagnosis.

In 1949, Soulie and associates[3] established certain criteria of combined ventricular hypertrophy on the basis of twenty-seven autopsied cases and thirty clinical cases. In only four of these cases were the findings pathognomonic of combined ventricular hypertrophy. In the others, presumptive diagnosis was based on various combinations of axis deviation, electrical position, and rotation. They felt that P-wave patterns were occasionally of significance. Levine and Phillips[4] noted the rarity of the diagnosis of combined ventricular hypertrophy in their electrocardiographic-anatomic studies.

MATERIAL

The necropsies between January, 1950, and June, 1951, at the Los Angeles County General Hospital were reviewed, and seventy-three cases with a right ventricular wall of at least 5 mm., a left ventricular wall of at least 14 mm., and a recent twelve-lead electrocardiographic tracing were found. A group of seventeen

From the Department of Medicine, College of Medical Evangelists and the Los Angeles County General Hospital.

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*Formerly intern, Los Angeles County General Hospital; Resident in medicine, Wadsworth General Hospital, Veterans Administration Facility, Los Angeles.

**Formerly instructor in medicine, College of Medical Evangelists; instructor in medicine, University of Southern California School of Medicine.

cases with a right ventricular wall measuring 3.5 to 4 mm. and a left ventricular wall 14 mm. or greater constituted the control group.

These ninety cases fell into 4 groups. Group A, the control group, consisted of seventeen cases of left ventricular hypertrophy in which the diagnosis of hypertensive heart disease had been made. Group B consisted of forty-six cases of combined ventricular hypertrophy in which the etiology was hypertensive heart disease. Most of these cases showed congestive failure at death. Group C was composed of nine cases in which cor pulmonale was diagnosed at necropsy and in which left ventricular hypertrophy was present. In only three of these cases was systemic hypertension present clinically. Group D consisted of eighteen cases of mixed valvular disease, mitral stenosis, and hypertension, and included one case of ventricular septal defect. These groups are summarized in Table I.

TABLE I.

GROUP	ETIOLOGY	NO. CASES	AVERAGE RIGHT VEN-TRICULAR WALL (MM.)	AVERAGE LEFT VEN-TRICULAR WALL (MM.)	L/R RATIO (AVERAGE)	AVERAGE HEART WT. (Gm.)
A	Hypertension	17	3.8	16.8	4.4	482
B	Hypertension	46	6.0	17.7	2.9*	573
C	Hypertension and cor pulmonale	9	7.4	15.1	2.1*	471
D	Mixed valvular heart disease	18	5.9	16.5	2.8*	567
All cases with right ventricular hypertrophy†		30	6.0	15.6	2.6	492
All cases with left ventricular hypertrophy†		33	4.9	17.2	3.5‡	560

*p is 0.001 when this group is compared to control Group A. "p" is the probability of difference between the means, calculated from Fisher's t.

†Exclusive of cases with combined ventricular hypertrophy.

‡Comparison of this ratio with the preceding one gives a p of <0.001.

METHOD

Only electrocardiograms taken on a photographic machine were used. Cases showing myocardial infarction and extensive or recent significant pulmonary emboli were discarded. No cases of bundle branch block or with QRS complexes of 0.11 second or greater duration were used. All cases with an "M" shaped complex in V_1 were discarded irrespective of the duration of the QRS complex.

The height of the components of the QRS complex in the precordial and augmented limb leads was measured and corrected for standardization. The ventricular activation time in V_1, V_2, V_5, and V_6 was measured with a magnifying glass in three complexes in each of these leads and the average recorded. Axis deviation and the presence of abnormal P waves in the standard leads were noted. Because of the administration of digitalis in a high percentage of these cases, ST-T patterns could not be adequately evaluated. The electrocardiographic data have been assessed against the criteria of Sokolow and Lyon.[5,6]

TABLE II. LEFT VENTRICULAR HYPERTROPHY

NUMBER OF CASES	GROUP A	GROUP B	GROUP C	GROUP D
	17	46	9	18
Criteria:				
R_{AVL} over 11 mm.	5	5	0	2
$R_{V5,6}$ over 26 mm.	2	3	0	1
R_{V5} plus S_{V1} over 35 mm.	9	9	0	3
$\frac{R/S_{V5}}{R/S_{V1}}$ over 100	2	8	0	0
$VAT^{*}_{V5 \text{ or } 6}$ 0.06 sec. or up	5	13	0	7
Number of cases with one criterion	13	23 (0.04)†	0 (<0.001)	8 (0.04)
Number of cases with two or more criteria	10	12 (0.01)	0 (<0.001)	3 (0.01)

*Ventricular activation time.

†p value.

TABLE III. RIGHT VENTRICULAR HYPERTROPHY

NUMBER OF CASES	GROUP A	GROUP B	GROUP C	GROUP D	TOTAL
	17	46	9	18	
Criteria:					
1. R_{V1} over 7 mm.	0	1	1	1	3
2. S_{V1} under 2 mm.	0	4	5	3	12
3. R_{V1} plus S_{V5} over 10.5 mm.	0	5	3	6	14
4. $S_{V5 \text{ or } 6}$ over 7 mm.	2	9	3	6	20
5. $R_{V5 \text{ or } 6}$ under 5 mm.	2	4	6	3	15
6. $R/S_{V5 \text{ or } 6}$ 1 or less	2	3	6	5	16
7. R_{AVR} 5 mm. or greater	0	1	0	1	2
8. R/S_{V1} over 1	0	4	5	3	12
9. $\frac{R/S_{V5}}{R/S_{V1}}$ 0.4 or less	0	3	3	3	9
10. P_2P_3 3 mm. or higher	2	4	5	4	15
11. VAT_{V1} 0.04 sec. or greater	0	4	6	3	13
Number of cases with one criterion	5	17 (0.02)	9 (<0.001)	10 (0.02)	
Number with two or more criteria	2	7 (0.08)	9 (<0.001)	7 (0.06)	

RESULTS

Tables II, III, and IV summarize the collected data with respect to the diagnosis of left and right ventricular hypertrophy. In Table II, the number of times each criterion of left ventricular hypertrophy was encountered is tabulated, and the number of cases in each group having either one, two, or more criteria is listed. In the control group, left ventricular hypertrophy was present electrocardiographically as often as in the report of Sokolow and Lyon.[5] When Group B (combined ventricular hypertrophy and hypertensive heart disease) was compared with the control group with respect to the frequency of left ventricular hypertrophy, the "p" values for single and double criteria were 0.04 and 0.01,

respectively. Thus, in this group where combined ventricular hypertrophy at necropsy was associated with previous hypertensive heart disease, there was impairment in the electrocardiographic recognition of left ventricular hypertrophy. Similarly in Group D, where the presence of right ventricular hypertrophy was associated with mixed valvular and hypertensive heart disease, interference with the recognition of left ventricular hypertrophy was noted.

In Group C, however, in which cor pulmonale was associated with a hypertrophied left ventricle, none of the electrocardiographic criteria of left ventricular hypertrophy was present. This was true in spite of three cases with left ventricular wall measurements of 16 mm. or greater.

Table III demonstrates the results with respect to electrocardiographic recognition of right ventricular hypertrophy as Table II did for left ventricular hypertrophy. The presence of one or more of the presumed criteria for electrocardiographic recognition of right ventricular hypertrophy in control Group A in five of seventeen cases not only reflects on the significance of the criteria, but directly influences the interpretation of the results in other groups. Although the left/right ratio in Groups B and D was significantly smaller than control Group A, the number of criteria of right ventricular hypertrophy did not differ significantly from the control group. Group C alone, using either one or two electrocardiographic criteria of right ventricular hypertrophy, differed significantly from the control group.

In Table IV the electrical position of the heart and the transition zone are listed for each group, for right ventricular hypertrophy, left ventricular hypertrophy, and combined ventricular hypertrophy. Statistical analysis of these figures is difficult, and only the general trends will be discussed.

Table V is an analysis of the ten cases in which criteria of right ventricular hypertrophy and left ventricular hypertrophy were present anatomically and electrocardiographically as well. The criteria listed in this table were the only ones present in these cases.

DISCUSSION

In this study it has been possible to correlate necropsy findings of ventricular wall hypertrophy with established criteria for electrocardiographic recognition of hypertrophy. Rosenman and associates[2] applied the criteria of Sokolow and Lyon[5,6] to a large series of clinically established cases of combined ventricular hypertrophy, but presented no close correlation with the presence of anatomic hypertrophy. Soulie and associates[3] had twenty-seven necropsies to correlate anatomic with electrocardiographic findings, but did not measure the specific changes associated with hypertrophy as suggested by Sokolow and Lyon.

In Table II it can be seen that right ventricular hypertrophy in the group with hypertensive heart disease (Group B) masked the diagnosis of left ventricular hypertrophy when one criterion was used. As might be expected, the greater number of criteria required for electrocardiographic recognition of left ventricular hypertrophy, the fewer the number of cases recognized. When two

TABLE IV. ELECTRICAL POSITION AND TRANSITION ZONE

	ELECTRICAL POSITION*						TRANSITION ZONE				
	H (%)	SH (%)	INT. (%)	SV (%)	V (%)	IND. (%)	V_2-V_3 (%)	V_3-V_4 (%)	V_4-V_5 (%)	V_5-V_6 (%)	V_6† (%)
Group A	35	35	12	12	6	0	6	41	35	12	6
Group B	33	22	20	17	7	2	4	20	52	20	4
Group C	0	0	0	33	67	0	0	11	22	22	45
Group D	0	28	17	17	39	0	0	6	50	33	11
% cases with right ventricular hypertrophy‡	3	27	0	30	40	0	0	7	23	37	33
% cases with left ventricular hypertrophy‡	42	27	18	9	3	0	6	33	54	6	0
% cases with combined ventricular hypertrophy	27	27	27	9	9	0	0	27	45	27	0

*H = Horizontal
SH = Semihorizontal
Int. = Intermediate
SV = Semivertical
V = Vertical
Ind. = Indeterminate
†No left ventricular complexes seen through V_6.
‡Exclusive of cases with combined ventricular hypertrophy.

TABLE V. ANALYSIS OF CASES DEMONSTRATING COMBINED VENTRICULAR HYPERTROPHY BOTH ELECTROCARDIOGRAPHICALLY AND ANATOMICALLY

CASE NO.		RIGHT HYPERTROPHY				LEFT HYPERTROPHY				
		$S_{V_{5-6}}$ OVER 7 mm.	R_{V_1} PLUS S_{V_5} OVER 10.5 mm.	$R_{V_{5-6}}$ UNDER 5 mm.	P_{2-3} LARGE	VAT V_{1-2} 0.04	R_{aVL} OVER 11 mm.	R_{V_5} S_{V_1} 35 mm.	$R_{V_{5-6}}$ OVER 26 mm.	$VAT_{V_{5-6}}$ 0.06
Group B	15A	—	—	—	—	Yes	Yes	—	—	—
	31	Yes	—	—	—	—	—	—	—	Yes
	33	—	—	—	Yes	—	—	—	—	Yes
	54	—	—	—	Yes	—	—	Yes	Yes	Yes
	60	Yes	Yes	—	Yes	—	Yes	Yes	—	Yes
	80	Yes	Yes	—	—	—	—	Yes	—	Yes
Group D	14	—	—	Yes	—	—	—	—	—	Yes
	27	Yes	Yes	—	—	—	—	—	—	Yes
	45	—	—	—	Yes	—	Yes	—	—	Yes
	58	Yes	Yes	—	—	—	Yes	Yes	—	Yes
Incidence		5	4	1	4	1	4	4	1	9

or more criteria were required for recognition of left ventricular hypertrophy, the large right ventricle was found to interfere significantly. The influence of right ventricular hypertrophy can also be seen in Table IV where, in Group B, the transition zone tended to shift to the left, and electrical positions of intermediate, semivertical, and vertical were encountered more often.

In Group C, in which hypertension was associated with cor pulmonale, all evidence of left ventricular hypertrophy was absent from the electrocardiogram. The electrical position and degree of clockwise rotation were those previously described in pure right ventricular hypertrophy. The anatomic findings in this group could be presumed to account for these data, as the left/right ratio in this group was significantly different from Group B ($p < 0.001$) and Group D ($0.01 > p > 0.001$) as well as from Group A.

In Group D (combined ventricular hypertrophy and mixed valvular disease) the recognition of left ventricular hypertrophy was impaired by the concomitant right ventricular hypertrophy when two or more criteria were required. These findings could be expected from the anatomic evidence, as the left/right ratio was similar to that in Group B (combined ventricular hypertrophy with hypertensive heart disease). The electrical positions and transition zone were intermediate between Groups B and C.

The diagnosis of right ventricular hypertrophy in these cases presents a more difficult problem. Rosenman[7] and McGregor[8] have stated in their studies on the genesis of the electrocardiogram that the R wave in V_1 is not necessarily a reflection of right ventricular activity, but may be totally or in part due to rotation. Fowler and associates[9] using simultaneous intracavity and chest leads presented more convincing evidence that the R in V_1 may be attributed to activation of the hypertrophied right ventricle. Somewhat indicative of the quandary of electrocardiographers is the number of criteria cited as evidence of right ventricular hypertrophy—eleven in Table III as compared to five in Table II for left ventricular hypertrophy.

Whenever right ventricular hypertrophy was diagnosed in the control group, Criteria 4, 5, 6, or 10 were present. These same criteria comprise a large number of the recognized criteria of right ventricular hypertrophy in Groups B, C, and D as well. Of these, Criteria 4, 5, and 6 may represent rotational change, and 10 relates to atrial rather than ventricular activity.

In Table III the electrocardiographic diagnosis of right ventricular hypertrophy in the presence of left ventricular hypertrophy was unimpaired only in Group C. Thus right ventricular hypertrophy resulting from cor pulmonale can be diagnosed more frequently than right ventricular hypertrophy resulting from rheumatic or hypertensive disease when left ventricular hypertrophy is also present. This correlates well with the highly significant anatomic differences between the groups.

The concept of ventricular predominance is given some support by this study. In Table IV the comparison of cases showing only right ventricular hypertrophy with those showing only left ventricular hypertrophy reveals that each group has a fairly typical distribution for both electrical position and transition zone.

Further, the left/right ratios of these two groups differed with a p of < 0.001. These observations, though, still leave unanswered the question of whether changes in the limb lead and unipolar electrocardiogram are mainly rotational or due to the differences in potentials of the opposing vectors of the right and left ventricles. Our data suggest that both of these factors are important; that the hypertrophied right ventricle becomes electrocardiographically apparent both by its increased activation potential and by the rotational changes produced.

The fact that the three etiologic groups of cases with combined ventricular hypertrophy had such wide differences in the manifest electrocardiographic diagnosis of right ventricular hypertrophy may be directly related to the anatomic evidence. It is true, however, that measurements of the diameter of the ventricular wall at necropsy may be a poor reflection of the dynamics of ventricular contraction or of the electrical potentials generated during life. Serial electrocardiograms of patients with left ventricular hypertrophy with several determinations of right ventricular pressure would offer further evidence as to the relative importance of hypertrophy and rotation.

The diagnosis of combined ventricular hypertrophy in this series was not made often. It is again apparent that Criteria 4, 5, 6, and 10 of Table III were those of greatest importance in the diagnosis of right ventricular hypertrophy in this group. Thus, when the electrocardiogram shows left ventricular hypertrophy, a transition zone shifted to the left or an atypical electrical position is often as good evidence of right ventricular hypertrophy as a detailed analysis using all of the above criteria. This type of diagnosis of combined ventricular hypertrophy fits closely with Groups II and III of Soulie and associates.[3]

It also follows that when left ventricular hypertrophy is overwhelmingly apparent by electrocardiogram, the anatomic presence of right ventricular hypertrophy will be extremely difficult to detect electrocardiographically, and at best, can only be surmised, as discussed above. Furthermore, as fourteen cases of the ninety exhibited no criteria of right ventricular hypertrophy or left ventricular hypertrophy, enlargement of the right and left ventricles can mutually mask the electrocardiographic findings associated with either.

SUMMARY

1. The precordial and augmented limb leads of seventy-three electrocardiograms from patients with necropsy evidence of combined ventricular hypertrophy have been analyzed.

2. When left ventricular hypertrophy occurred as a result of hypertensive or aortic valve disease, its recognition was slightly impaired by the concomitant right ventricular hypertrophy. Left ventricular hypertrophy associated with cor pulmonale is hidden electrocardiographically.

3. Right ventricular hypertrophy occurring as a result of hypertensive heart disease or mitral disease was masked by the concomitant left ventricular hypertrophy. Cor pulmonale occurring with left ventricular hypertrophy was apparent.

4. The data suggest that rotational effects and the potentials of the respective ventricular walls are both important in the recognition of right ven-

tricular hypertrophy in the presence of left ventricular hypertrophy. The electrocardiographic diagnosis of right ventricular hypertrophy in the presence of left ventricular hypertrophy may be suspected when atypical electrical positions are present, or the transition zone is shifted to the left.

5. The diagnosis of combined ventricular hypertrophy is difficult and was apparent only in ten cases of seventy-three. In these cases, right ventricular hypertrophy was recognized by the rotational changes.

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REFERENCES

1. Langendorf, R., Hurwitz, M., and Katz, L. N.: Electrocardiographic Patterns of Combined Ventricular Strain, Brit. Heart J. **5**:27, 1943.
2. Roseman, R. H., Krause, S., Hwang, W., and Katz, L. N.: The Electrocardiographic Diagnosis of Combined Left and Right Ventricular Strain, Am. Heart J. **40**:453, 1950.
3. Soulie, P., Laham, J., Papanicolis, I., and Voci, G.: Les principaux types electrocardiographiques de surcharge ventriculaire combinee, Arch. d. mal. du coeur. **42**:791, 1949.
4. Levine, H. D., and Phillips, E.: An Appraisal of the Newer Electrocardiography: Correlations in One Hundred and Fifty Consecutive Autopsied Cases, New England J. Med. **245**:833, 1951.
5. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **37**:161, 1949.
6. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Right Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **38**:273, 1949.
7. Rosenman, R. H.: Observations on the Genesis of the Electrocardiogram, Am. Heart J. **40**:522, 1950.
8. McGregor, M.: The Genesis of the Electrocardiogram of Right Ventricular Hypertrophy, Brit. Heart J. **12**:351, 1950.
9. Fowler, N. O., Westcott, R. N., and Scott, R. C.: The Q Wave in Precordial Electrocardiograms Overlying the Hypertrophied Right Ventricle: Intracavity Leads, Circulation **5**:441, 1952.

ON THE RESPONSE OF ECTOPIC AURICULAR TACHYCARDIAS TO VAGUS STIMULATION

David Scherf, M.D., Serge Blumenfeld, M.D., Paul Mueller, M.D., and William H. Beinfield, M.D.

New York, N. Y.

Topical application of aconitine on the dog's auricle or ventricle leads, respectively, to the appearance of auricular or ventricular tachycardias with rates of 250 to 300 beats per minute.[15,19] Faradic vagal stimulation produces a further increase in rate of such an auricular tachycardia and when the rate exceeds 600, auricular fibrillation occurs. This response of the auricular ectopic center to vagal stimulation identifies the tachycardia as auricular flutter.[15] Further experiments demonstrated that this tachycardia is produced by impulse formation in the area on which aconitine had been applied and not by a circus movement mechanism.[20] Rapid discharge of stimuli in a center may also be assumed to be the mechanism of most, if not all, paroxysmal tachycardias. Clinical experience, however, shows that in many instances of paroxysmal tachycardia one can readily abolish the attack by one of several vagal reflexes, particularly carotid sinus pressure, whereas this same effect has not been obtained in auricular flutter. Accordingly, it was concluded that the finer mechanism of stimulus formation in flutter differs from that in paroxysmal tachycardias.[22] On the other hand, some have assumed the difference in response of these two main forms of auricular tachycardia (paroxysmal tachycardia and flutter) to vagal stimulation to be only a function of the auricular rate. When the rate of the tachycardia is below a certain critical level, vagal stimulation produces asystole; when it is above this level such stimulation increases the rate or even leads to the appearance of auricular fibrillation.[8]

In view of this difference of opinion we investigated the effect of vagal stimulation on auricular arrhythmias caused by topical application of aconitine.

METHOD

The experiments were performed on twenty-eight dogs with the same technique as in the papers of our group quoted above. A few crystals of aconitine were applied to the outer wall of the appendix of the right auricle. The right

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.

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vagus nerve was severed in the neck and, when required, the peripheral end was stimulated with a strong faradic current from a Cambridge inductorium. In most tracings the duration of the vagal stimulation can be recognized by a slight distortion of the electrocardiographic tracing. The electrocardiogram was always registered in Lead II.

After the application of aconitine, auricular flutter and occasionally auricular fibrillation appeared within two to six minutes. This is the end result caused by the topical application of this substance. Therefore, any change in the electrocardiogram during the vagal stimulation before the appearance of flutter was due either to the increased vagal tone or to an early aconitine effect or a combination of both, the vagal and the aconitine influence. However, disappearance of an arrhythmia, temporary increase, or slowing of the rate during or immediately after the vagal stimulation could not be regarded as being due to aconitine alone, but had to be attributed to an additional vagal effect. In the accompanying illustrations, the beginning and sometimes also the end of the vagus stimulation are marked by an arrow.

RESULTS

Tracings obtained in a typical experiment are represented in Fig. 1. In Fig. 1,*A*, registered immediately after the application of aconitine on the right auricular appendix, the effect of faradic stimulation of the right vagus is seen. The response is identical with that found in a control heart. A long asystole appears with the occasional escape of a sinus beat. The P-R interval of the sinus beats during vagal stimulation is longer. After the vagal stimulation, the Ta wave of a few sinus beats is accentuated. The tracing of Fig. 1,*B*, was taken forty-five seconds later when regular sinus rhythm still prevailed. Here again, the sinus node activity slows during the vagal stimulation and a marked bradycardia appears; in addition, premature P waves are visible in the T waves of every sinus beat. After the vagal stimulation was discontinued, two auricular extrasystoles are seen which are conducted to the ventricles. Consequently we are dealing with auricular extrasystoles appearing only during vagal stimulation and immediately after its cessation. Fig. 1,*C*, shows the effect of vagal stimulation fifteen seconds after Fig. 1,*B*, had been obtained. At this time, auricular extrasystoles were present before the vagal stimulation. During the stimulation there is a definite slowing of the sinus rhythm and the auricular extrasystoles vanish. However, an ectopic rhythm appears with a change in the form of the P waves, which are diphasic. Many of these ectopic auricular beats are blocked before reaching the ventricle, but some are conducted and when this happens, a characteristic auricular arrhythmia appears. The duration of successive auricular cycles during the vagal stimulation in Fig. 1,*C*, measures: 0.34, 0.42, 0.38, 0.40, *0.36*, 0.56, *0.38*, 0.56, *0.36*, and 0.76 second. (The auricular intervals with QRS complex between the P waves are printed in italics.) Thus, there is a distinct prolongation of the auricular intervals following a conducted beat.

The tracing of Fig. 1,*D*, was registered twenty seconds after Fig. 1,*C*. Auricular extrasystoles are still present (second and third complex). Electrical interference distorting the tracing can be seen at the beginning of the vagal stimulation but this disappeared when the stimulated nerve was lifted from its bed. During the vagal stimulation an increase of rate of the ectopic rhythm is visible in the center of the tracing. The auricular periods shorten from 0.48 to 0.32 second. During this auricular tachycardia a slight arrhythmia is noticeable. A definite prolongation of the auricular period following a ventricular beat again can be seen. The auricular tachycardia ends after discontinuation of the vagal stimulation but reappears immediately after the following beat which exhibits a normal P wave. Fig. 1,*E*, and Fig. 1,*F*, were taken twenty and forty seconds later, respectively. The tachycardia persists and the auricular rate gradually increases. In Fig. 1,*E*, it is 200 per minute before and during the vagal stimulation. In Fig. 1,*F*,

A.

B.

C.

D.

E.

F.

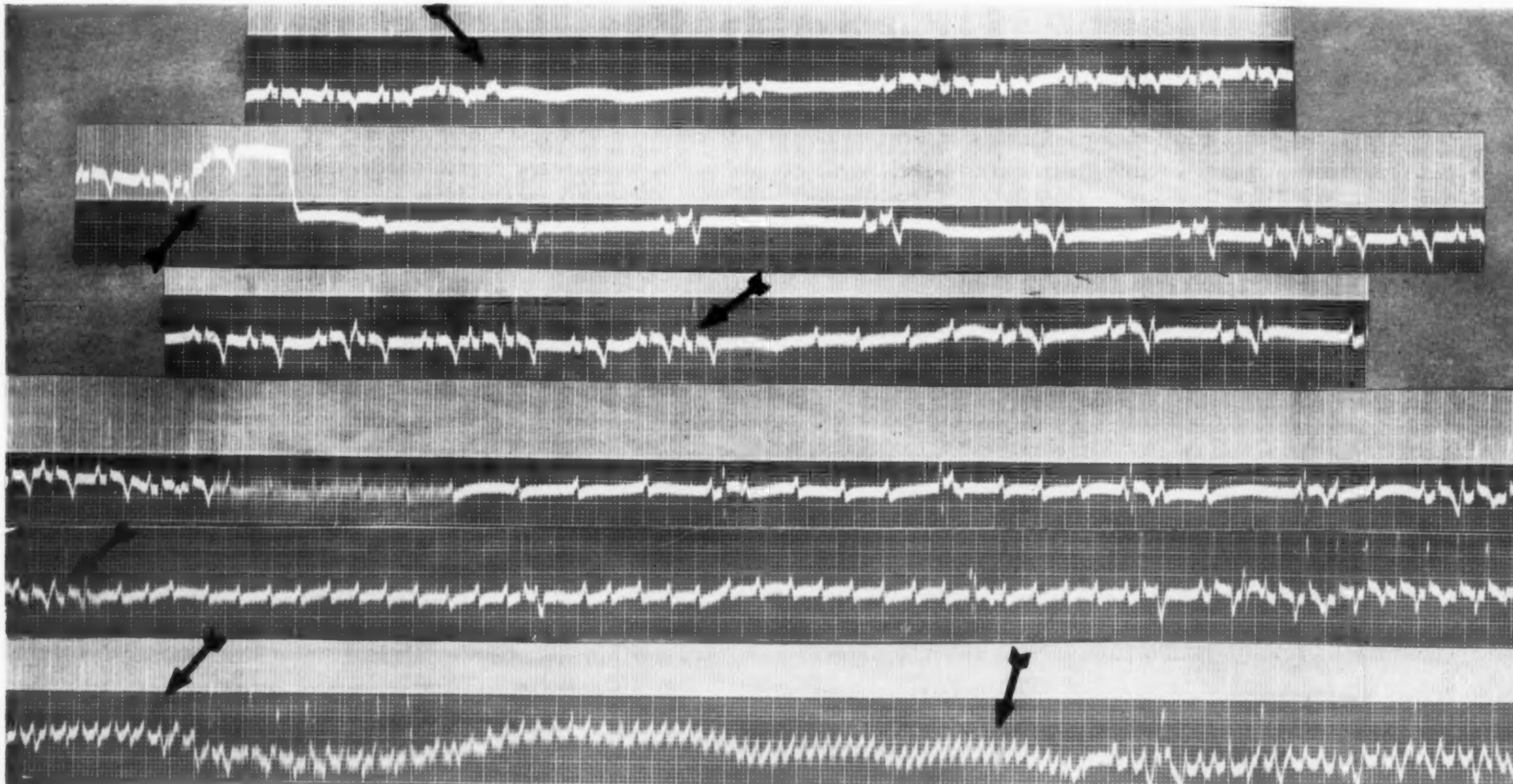

Fig. 1.—*A*, The effect of vagal stimulation immediately after application of aconitine on the appendix of the right auricle. Note the absence of a Ta wave in the first sinus beat after the vagal stimulation and the accentuated Ta waves in the following beats. *B*, The appearance of blocked auricular extrasystoles during vagal stimulation. *C* demonstrates the appearance of an ectopic rhythm during the same measure. Note the marked prolongation of the auricular intervals following an escaped ventricular beat. Vagal stimulation accelerates the ectopic rhythm in *D* but not in *E*. The rate is increased in *F*. Shortly after discontinuation of the vagal stimulation, the ectopic tachycardia disappears for a very short period in *E* and *F*.

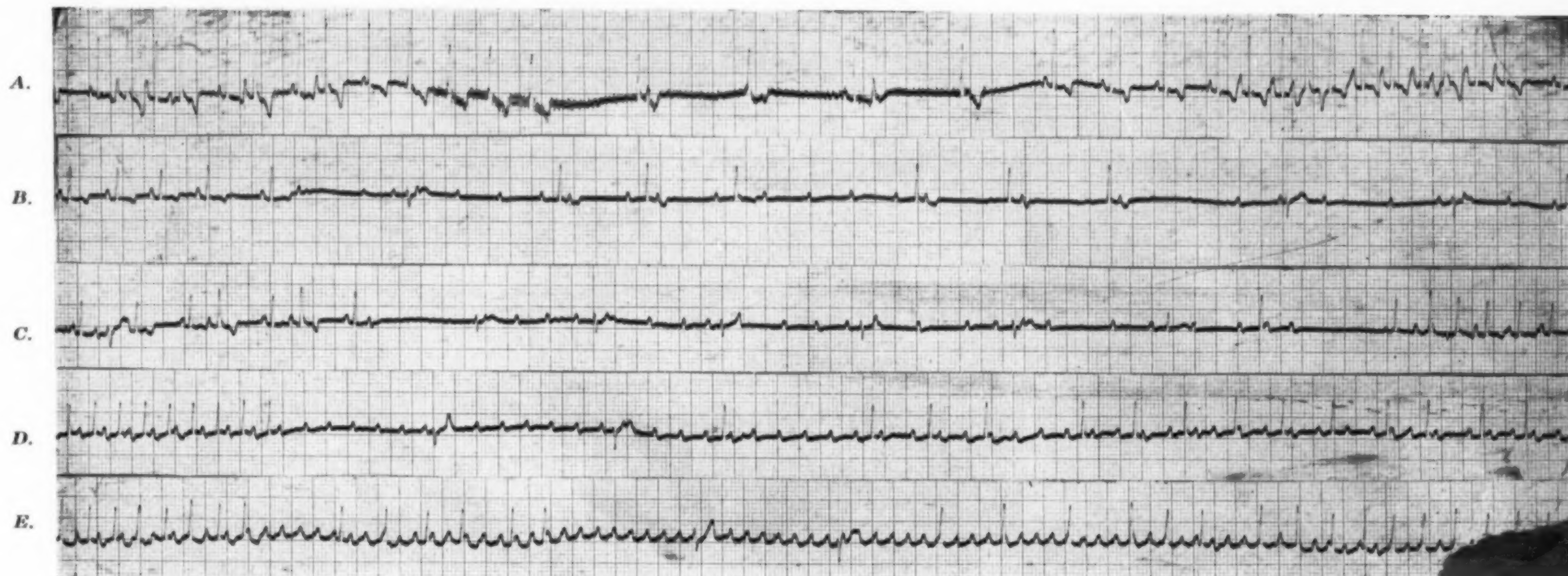

Fig. 2.—Auricular extrasystoles are inhibited by vagal stimulation in *A*, and an ectopic auricular rhythm appears during vagal stimulation in *B*. The following tracings (*C* to *E*) show the vagal effects on the increasing auricular rate.

it is 500 before and it increases to 600 per minute during the vagal stimulation. In Fig. 1,*F*, as in Fig. 1,*E*, the rapid auricular tachycardia stops shortly after the end of the vagal stimulation but recurs after the next sinus beat.

This experiment, which is characteristic of many others, shows that vagal stimulation may lead to an increase of rate of the ectopic rhythm quite independently of the rate of the existing sinus rhythm. An increase of rate appeared in Fig. 1,*D*, when the ectopic center formed only an occasional extrasystole and when the ectopic rate was only 125 per minute at the beginning of the vagal stimulation. Vagal stimulation during an ectopic tachycardia of 200 per minute in Fig. 1,*E*, did not change the rate. Auricular extrasystoles appear during vagal stimulation (Fig. 1,*B*) but more often they are inhibited (Fig. 1,*C* and *D*) and appear in increased numbers immediately afterward.

Fig. 2,*A*, taken twenty seconds after application of aconitine, shows at the beginning several auricular extrasystoles after every sinus beat. The extrasystoles disappear during the vagal stimulation with the exception of two blocked ones; they appear in increased numbers immediately after stimulation ends. Thirty seconds later, during vagal stimulation, auricular ectopic beats appear (Fig. 2,*B*) with a faster rate than the sinus beats before the stimulation. The rate of the sinus beats varies between 136 and 150 per minute, the rate of the ectopic rhythm during vagal stimulation is 158 to 214 per minute. One notices the prolongation of the auricular period after an escaped ventricular beat (Fig. 2,*C*), extending over two auricular intervals. The number of auricular extrasystoles increases after the vagal stimulation. In Fig. 2,*D*, an auricular tachycardia exists with a rate of 250 beats per minute. This rate does not change during the vagal stimulation. At the beginning of Fig. 2,*E*, the auricular rate is 300; during vagal stimulation it is increased to 420, but remains at 380 per minute after the vagal stimulation has been discontinued.

This experiment shows the inhibition of auricular extrasystoles during vagal stimulation. With more advanced effect of aconitine, however, during vagal stimulation an ectopic auricular tachycardia appears (Fig. 2,*D*) which shows a gradual increase in rate. With a rate of 250 per minute the vagal stimulation remains without effect, while a few seconds later vagal stimulation of the same strength leads to an increase of rate, when the auricles were beating 300 per minute. In previous publications of the senior author (D.S.) many instances are shown in which vagal stimulation increased the auricular rate with the auricles beating only 250 per minute or less.[15,20,22]

In some experiments the vagal stimulation remained without influence on the rate of an ectopic aconitine tachycardia even when the auricular rate was extremely rapid (Fig. 3). In Fig. 3,*A*, vagal stimulation immediately following application of aconitine showed the same results as seen in normal hearts, that is, only inhibition. Two minutes later (Fig. 3,*B*) a sinus rate of 150 per minute existed. Vagal stimulation now caused the appearance of an ectopic auricular rhythm exhibiting P waves of a different form but showing also a rate of 150 per minute. Following escaped ventricular beats, the auricular interval is prolonged. An auricular bigeminy exists in Fig. 3,*C*, since an auricular extrasystole follows each sinus beat with a coupling of 0.32 second. During vagal stimulation a regular ectopic tachycardia appears with a rate of 186 per minute. In Fig. 3,*D*, the bigeminy persists, the coupling now amounting to 0.26 second. This tracing was obtained forty seconds after the tracing of Fig. 3,*C*. This time during the vagal stimulation a regular auricular tachycardia appears with a rate of 230 per minute. In the following tracing (Fig. 3,*E*), obtained twenty seconds later, a continuous tachycardia exists with a rate of 272 per minute. This rate persisted during vagal stimulation. The same holds for Fig. 3,*F*, which was obtained a few seconds later when the rate was 500 per minute.

This independence of the effect of vagal stimulation from the rate of the existing tachycardia is evident in another experiment (Fig. 4). Here the right vagus nerve was stimulated twice in short succession. The tracing is distorted by the faradic current but all necessary details are clearly visible. The aconitine had elicited a tachycardia with a rate of 220 per minute and there is an alternation of successive cycle length which is common in auricular flutter caused by faradization or aconitine. The first vagal stimulation stopped this tachycardia and was immediately discontinued. Vagal stimulation was resumed after the next sinus beat and this time the rate increases for a few cycles to 300 per minute. After the vagal stimulation the rate dropped to the same level as at the beginning of the tracing.

Finally, in the experiment from which Fig. 5 has been obtained an ectopic tachycardia with a rate of 200 per minute appeared after aconitine application. Vagal stimulation stopped this tachycardia but series of extrasystoles follow each sinus beat. The extrasystoles are coupled and the rate had increased to 240 per minute. After cessation of the vagal stimulation the same ectopic tachycardia appeared as before the stimulation. This tracing demonstrates one of the few instances where vagal stimulation transformed a regular ectopic tachycardia into extrasystoles with constant coupling.

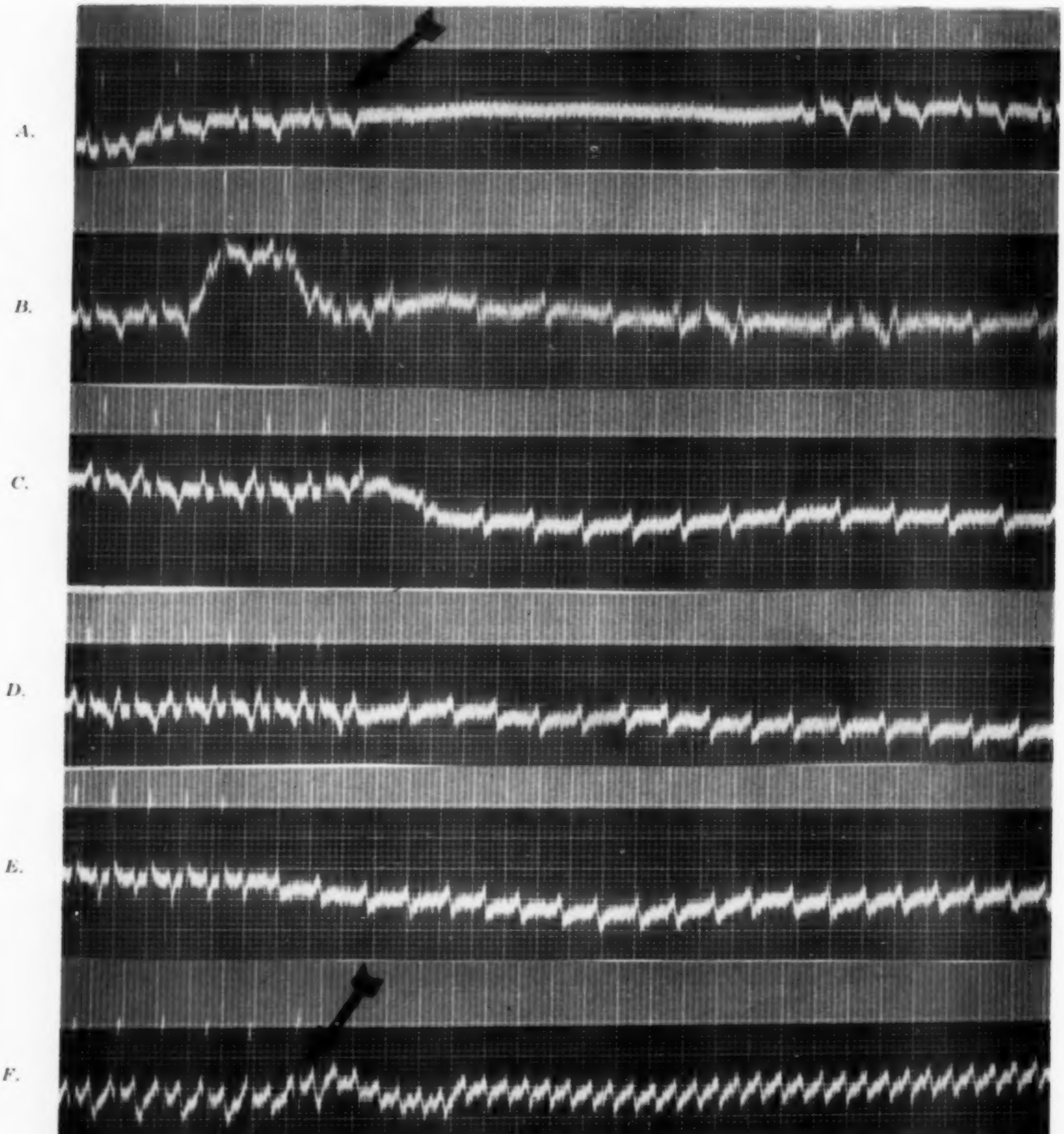

Fig. 3.—*A*, the effect of vagal stimulation immediately after the application of aconitine; an ectopic rhythm appears during vagal stimulation in *B*. Auricular bigeminy is transformed into an ectopic auricular tachycardia with increasing rates in *C* and *D*. In *E* and *F*, in spite of higher rates of the ectopic tachycardia, vagal stimulation does not change its rate.

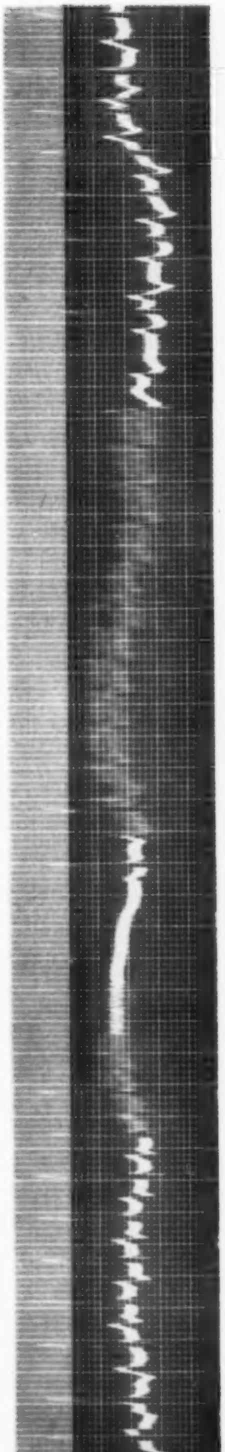

Fig. 4.—Vagal stimulation stops an ectopic auricular tachycardia and, when repeated shortly afterward, increases its rate.

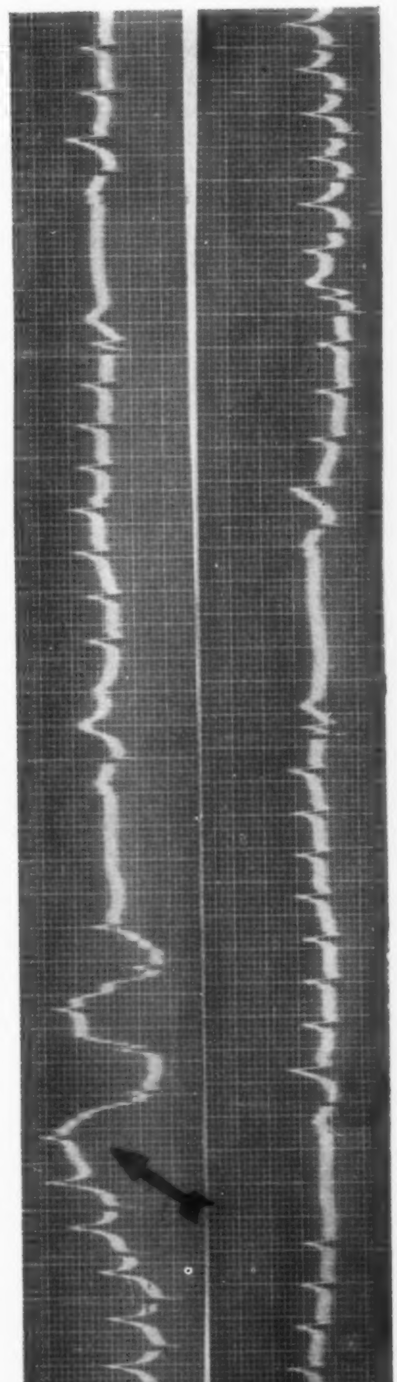

Fig. 5.—Vagal stimulation transforms an ectopic auricular tachycardia into extrasystoles with fixed coupling and increased rate. The two tracings are continuous.

DISCUSSION

These experiments show that vagal stimulation following topical application of aconitine caused the appearance of an ectopic rhythm at a time when with aconitine alone no changes could be seen as yet in the electrocardiogram. This abnormal rhythm had the same rate as the existing sinus rhythm or was a little faster. Continued vagal stimulation caused a temporary acceleration of the activity of the ectopic center. At this time, spontaneous auricular extrasystoles often appeared which were coupled. Vagal stimulation usually abolished the extrasystoles and an accelerated ectopic rhythm appeared in their place. After cessation of the vagal stimulation the extrasystoles reappeared, always in temporary increased numbers. Only rarely did extrasystoles appear during stimulation of the vagi (Fig. 1,*B*). Soon the sinus rhythm was replaced by a continuous ectopic rhythm. The rate of this rhythm gradually became faster and soon reached values above 300 per minute (auricular flutter). Auricular fibrillation occasionally appeared at this time, particularly following vagal stimulation. In rare instances vagal stimulation transformed an ectopic tachycardia into extrasystoles with fixed coupling (Fig. 5). At no time was the response to vagal stimulation dependent upon the rate of the ectopic tachycardia. Actually the experiments show clearly that, even with a slow rate of the ectopic rhythm, vagal stimulation led to a faster rate, while during a much faster ectopic tachycardia vagal stimulation may cause no change.

The effect of vagal stimulation upon the sinus rhythm is, under normal conditions, purely inhibitory. On rare occasions an increase of rate has been noted. This was explained by simultaneous stimulation of sympathetic fibers but is more readily understood since it became known that acetylcholine can increase the rate of a impulse-forming center and may lead to rapid ectopic rhythms.[18]

The usual effect of an increased vagal tone on extrasystolic rhythms and paroxysmal tachycardias is also inhibitory and a good illustration of this is the termination of an attack of paroxysmal tachycardia by carotid sinus pressure. Here again, however, exceptions have been noted and occasionally extrasystoles and paroxysmal tachycardias have appeared in man during carotid pressure.[1,21,23]

Experimentally a notable instance of an increase of the number of *ventricular* extrasystoles during vagal stimulation has been observed following intravenous administration of minute amounts of aconitine. During vagal stimulation they appeared with great regularity, even if they were absent before, or their number increased, or they were reproduced again after they had subsided.[11] On the other hand, *auricular* extrasystoles, which were shown in these experiments[12] to originate in the sinus node, were inhibited during the vagal stimulation but they appeared in increased numbers following cessation of the stimulation. Often auricular flutter or fibrillation appeared three to four seconds after the end of the vagal stimulation. These effects were strikingly similar to those described above following topical application of aconitine. The disappearance of the coupled auricular extrasystoles during vagal stimulation was partly explained by the fact that coupled beats cannot appear without a

preceding "initiating" beat. If auricular extrasystoles remained absent during vagal stimulation even when sinus beats escaped, we may assume that a diminished excitability made it impossible for the auricle to respond to ectopic stimuli.[12]

The effect of vagal stimulation during experimental flutter is complex. It has been carefully studied by Lewis and associates,[6] who elicited flutter by electric stimulation of the auricles. These authors found that occasionally even powerful stimulation of the vagus nerve remained without any influence on the rate of the fluttering auricle. In most instances, however, the rate gradually increased during the stimulation and gradually decreased to its previous level after stimulation ended. Often auricular fibrillation appeared. In rare instances vagal stimulation terminated this type of auricular flutter when a weak faradic current was employed or at the very beginning of application of a strong current. It is important to note that flutter elicited by aconitine responds in a similar way. Usually the rate is increased, sometimes it remains unchanged and rarely is flutter abolished (Fig. 1,*E* and *F*). The latter event happened only shortly after discontinuation of a prolonged vagal stimulation for a fraction of a second.

The increase of the flutter rate during vagal stimulation is a paradoxic and, therefore, most interesting effect. This phenomenon had been studied by Rothberger and Winterberg[10] who explained the flutter by rapid stimulus formation in a center. These authors found it impossible to assume that the rate of impulse formation is increased because of a higher vagal tonus as only the inhibitory effect of the vagus was known at that time. They left the phenomenon unexplained but considered it probable that the shortening of the refractory phase of the auricle during vagal stimulation is responsible in some way. Lewis and associates[6] offered two explanations for the increase of rate in flutter during the vagal stimulation. According to them, the shortening of the refractory period of the auricle during stimulation of the vagal nerve leads to the disappearance of islands of refractory tissue in the path of the circulating central wave. This makes the central wave pursue its path in a less sinuous way and, therefore, with an increased rate. Another possibility discussed by Lewis was the assumption that under the influence of vagal stimulation the central wave would follow an ever-shorter path around the venae cavae.

Lewis also gave an explanation for the occasional disappearance of flutter during vagal stimulation. If the vagi are stimulated, the shortened refractory phase of the auricles removes barriers of refractory tissue and makes the central wave circulate so much faster that the gap of excitable tissue in front of the central wave disappears so that "its head meets its tail," in other words, the circulating wave encounters refractory tissue and stops. This effect is counteracted by another one which tends to widen the gap, since the general shortening of the refractory period makes all muscle fibers recover faster. The final outcome will depend on whether one effect is more pronounced than the other. If these mechanisms were responsible for the disappearance of flutter during vagal stimulation, one should note in the tracings an increase of rate before the flutter disappears. Actually the tracings published by Lewis and associates show a slowing of the rate as measured by the length of the last, or the last few cycles. This slowing is understandable if we explain flutter by a rapid impulse formation in a center.

Our previous studies demonstrated that auricular (or ventricular) flutter caused by focal application of aconitine are not due to a circus movement but due to stimulus formation in a center.[15,20] The increase of the ectopic auricular rate during vagal stimulation therefore could be attributed to one of the following two mechanisms: (1) an increase in rate of stimulus formation or (2) a shortening of the refractory period leading to a more rapid response to a continuous stimulus. If a continuous stimulus existed, the rate of response would depend on the speed with which the muscle recovers from refractoriness. Since vagal stimulation shortens the refractory period to as much as one-fifth of its normal duration, it is understandable that during vagal stimulation auricular rates of as much as 3,000 per minute have been observed. It must be stressed that in the experiments presented in this report an increase of rate of the ectopic center was observed at a time when the long diastolic periods between the single P waves a priori ruled out the possibility of a circus movement. A circus movement mechanism can only be considered in a continuous succession of auricular waves with very rapid rates.

The experiments reported here show that aconitine flutter which is caused by rapid stimulus formation and not by a circus movement responds to vagal stimulation in the same way as postfaradic flutter. We are unable to explain these different effects on the basis of the available data. We know that acetylcholine enhances the formation of aconitine extrasystoles.[12] It is possible that different amounts of acetylcholine act on a stimulus formation center in different ways. Acetylcholine synthesis is influenced by the amount of acetylcholine available and it has been shown that acetylcholine added to a bath containing actively beating auricles may depress their activity; on the other hand, when acetylcholine is added to a bath containing auricles which had ceased to beat, it may initiate renewal of the beats.[2] It is also probable that the action of acetylcholine does not depend on its concentration only but also on the condition of the cell.

The type of response to the vagal stimulation could never be foreseen. Parallel clinical observations are those cases in which carotid pressure caused or abolished ventricular paroxysmal tachycardias in the same person[24] and the experimental experience that mere vagal stimulation in an otherwise normal heart may lead to auricular fibrillation.[9] Auricular fibrillation in man, caused by taking a deep breath, has been repeatedly observed.[16]

In a previous communication it was pointed out that faradic stimulation of one of the vagal nerves in the neck or intravenous injection of acetylcholine changed, in the dog, the form of the auricular electrocardiogram as registered in the standard leads.[23] There appears a marked depression of the P-R segment due to an accentuation of the Ta wave. This phenomenon which appears for a series of beats following the end of the vagal stimulation was explained by the shortening of the monophasic action current of the auricular muscle as consequence of vagal stimulation.[3] It is known, however, that the length of diastole also influences the duration of the monophasic action current; it is shortened with higher rates, it is lengthened with a slowing of rate. The prolonged refractory phase of the first beat following a prolonged diastole and the shortening of the refractory phase in tachycardias are well-known phenomena. It was there-

fore anticipated that the first beat after a long pause caused by vagal stimulation would not show the shortening of the monophasic action current and would therefore not exhibit a pronounced Ta wave, or the latter would be less pronounced than in the following beats. Figs. 1,*A*, and 3,*A*, show that this was actually the case. The P-R segment of the first sinus beat after the long pause is in the zero line while the following beats show a depression.

The records also demonstrate another interesting phenomenon which has been observed in the experimental animal by Erlanger and Blackman.[4] We refer to the short interauricular interval in partial or complete heart block when it embraces a QRS complex and the prolongation of the following auricular cycle.[14] This phenomenon is clearly present in many of our tracings and it is evident that the short interauricular interval with a QRS complex actually is of normal duration, while the following one is prolonged.

Most authors agree with the first observers that the prolongation of the auricular cycle following a ventricular systole is due to a reflex increase of vagal tone because of the rise of pressure in aorta and carotid sinus immediately after the ventricular systole.

The fact that this phenomenon is very pronounced in our tracings may be due to its appearance during vagal stimulation. In addition, it has been demonstrated that under the influence of aconitine vagal effects on the auricle are markedly increased, leading even in the early stages of intoxication to a complete disappearance of contraction of the auricles without any visible changes in the electrocardiogram.[12] The latter effect appears even after severance of both vagi in the neck and it is abolished immediately by atropine. It was therefore attributed to a stimulation of the peripheral vagal end apparatus.[12] It is, however, of interest that in the experiments presented here the ectopic center is so readily slowed down by a short lasting reflex increase of vagal tonus after one of the vagus nerves had been severed, while more prolonged direct vagal stimulation leads so often to an increase of rate.

At this juncture a few remarks concerning extrasystolic stimulus formation caused by topical application of electrolytes and different other substances seem justified. The appearance of extrasystoles due to chemical stimuli has been known for many years.[5] Most experiments were performed in the preelectrocardiographic era and the type of stimuli formed was not analyzed. More recently, the extrasystolic arrhythmias caused by focal application of sodium and barium chloride, strophanthin and digitoxin, aconitine, veratrine, and acetylcholine have been studied on the dog heart in situ.[7,13,17,18] The investigations showed that the resulting arrhythmias are not due to local currents of injury from the area on which the substance had been applied. Rather, a specific ion effect could be found for each of the above-named substances produced a different and characteristic pattern of abnormal stimulus formation. For example, ventricular[14] tachycardias caused by the application of sodium chloride were regular whereas tachycardias caused by the topical application of barium chloride were irregular. This irregularity was of the same kind as that seen when barium was injected intravenously. Arrhythmias caused by sodium chloride, veratrine, or acetylcholine appeared immediately while those due to digitalis, strophanthin, and

barium chloride appeared after a latent period of several minutes. This latency was greater with digitoxin as compared to strophanthin. Aconitine caused very rapid regular tachycardias and often fibrillation, while veratrine elicited much slower tachycardias and parasystole.[17] Veratrine never caused coupled extrasystoles while they were commonly seen after the other substances.[21]

The findings following topical application of the above-named substances are similar to those seen after intravenous administration. Topical application of a substance on the surface of the heart may therefore serve as a useful method for pharmacologic and physiologic studies.

SUMMARY AND CONCLUSIONS

In experiments on dogs, auricular ectopic rhythms were initiated by topical administration of aconitine. The changes of these rhythms during vagal stimulation were studied.

The earliest change caused by topical application of aconitine to the auricle is the appearance of auricular extrasystoles. They usually vanished during vagal stimulation but invariably appeared in increased number immediately following this procedure. Therefore, vagal stimulation had on these extrasystoles the same influence as on those which were caused by intravenous administration of minute doses of aconitine. In rare instances vagal stimulation caused the appearance of auricular extrasystoles with fixed coupling or changed an ectopic tachycardia into extrasystoles with fixed coupling.

A little later regular ectopic rhythms were initiated by vagal stimulation. The rate of these relatively slow rhythms as well as of fast rhythms which appeared later was usually increased during the vagal stimulation. On the other hand, an effect of the vagal stimulation on the ectopic rhythms was sometimes missing even with exceedingly high rates of ectopic stimulus formation. In rare instances the ectopic auricular tachycardia and auricular flutter were stopped by vagal stimulation.

Thus the auricular flutter elicited by topical application of aconitine responded to vagal stimulation exactly in the same unpredictable way as flutter caused by electrical stimulation. There is no relation between mode of vagal action and existing rate of the ectopic center.

The absence of an accentuated Ta wave in the first beat following vagal stimulation is described and an explanation is given for this phenomenon.

Changes of auricular rates during vagal stimulation caused by escaped ventricular beats are described; their relation to the aconitine action and vagal stimulation is analyzed.

Heterotopic stimulus formation caused by topical application of different substances on the exposed heart of the dog is shortly reviewed.

REFERENCES

1. Blumenfeld, S., Schaeffeler, K. T., and Zullo, R. J.: An Unusual Response to Carotid Sinus Pressure, AM. HEART J. **41**:319, 1951.
2. Burn, J. H.: A Discussion of Local Hormones, Proc. Roy. Soc., B. **137**:281, 1950.
3. Churney, L., Ashman, R., and Biggins, C. H.: Effect of Vagus on the Monophasic Action Potential of Auricular Muscle, Proc. Soc. Exper. Biol. & Med. **70**:123, 1949.
4. Erlanger, J., and Blackman, J. R.: Further Studies in the Physiology of Heart Block in Mammals, Heart **1**:177, 1909.
5. Langendorff, O.: Studien über Rhythmik und Automatie des Froschherzens, Arch. Anat. Physiol, Suppl., p. 1, 1884.
6. Lewis, T., Drury, A. N., and Bulger, H. A.: Flutter and Fibrillation; the Effects of Vagal Stimulation, Heart **8**:141, 1921.
7. Piccione, F. V., and Scherf, D.: The Rhythmic Formation of Coupled Beats and Paroxysmal Tachycardias in the Outer Layers of the Myocardium, Bull. New York M. Coll. **3**:93, 1940.
8. Prinzmetal, M., Corday, E., Oblath, R. W., Kruger, H. E., Brill, I. C., Fields, J., Kennamer, S. R., Osborne, J. A., Smith, L. A., Sellers, A. L., Flieg, W., and Finston, E.: Auricular Flutter, Am. J. Med. **11**:410, 1951.
9. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, J. Exper. Med. **17**:429, 1913.
10. Rothberger, C. J., and Winterberg, H.: Ueber Vorhofflimmern und Vorhofflattern, Arch. f. d. ges. Physiol. **160**:42, 1914.
11. Scherf, D.: Untersuchungen zur Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, Ztschr. f. d. ges. exper. Med. **65**:189, 1929.
12. Scherf, D.: Untersuchungen ueber die Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, Ztschr. f. d. ges. exper. Med. **65**:222, 1929.
13. Scherf, D.: Experimental Digitalis and Strophanthin Extrasystoles, Exper. Med. & Surg. **2**:70, 1944.
14. Scherf, D.: Periodic Changes in the Form of the P Waves in Partial Heart Block, AM. HEART J. **29**:213, 1945.
15. Scherf, D.: Studies on Auricular Tachycardia Caused by Aconitine Administration, Proc. Soc. Exper. Biol. & Med. **64**:233, 1947.
16. Scherf, D., and Boyd, L. J.: Clinical Electrocardiography, ed. 3, London, 1948, William Heinemann, Ltd.
17. Scherf, D., and Chick, F. B.: Experimental Parasystole, AM. HEART J. **42**:212, 1951.
18. Scherf, D., and Chick, F. B.: Abnormal Cardiac Rhythms Caused by Acetylcholine, Circulation **3**:764, 1951.
19. Scherf, D., Morgenbesser, L. J., Nightingale, E. J., and Schaeffeler, K. T.: Mechanism of Ventricular Fibrillation, Cardiologia **16**:232, 1951.
20. Scherf, D., Romano, F. J., and Terranova, R.: Experimental Studies on Auricular Flutter and Auricular Fibrillation, AM. HEART J. **36**:241, 1948.
21. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, London, 1953, William Heinemann, Ltd.
22. Scherf, D., and Terranova, R.: Mechanism of Auricular Flutter and Fibrillation, Am. J. Physiol. **159**:137, 1949.
23. Scherf, D., and Terranova, R.: Changes of the Ta Wave in Standard Leads Following Stimulation of the Vagus Nerves, Proc. Soc. Exper. Biol. & Med. **74**:353, 1950.
24. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, 1927, Wilhelm Engelmann.

STUDIES WITH INTRAVENOUS GITALIN. I.

CLINICAL AND ELECTROCARDIOGRAPHIC OBSERVATIONS

OLGA M. HARING, M.D., AND ALDO A. LUISADA, M.D.
CHICAGO, ILL.

DIGITALIS has been the drug of choice in the treatment of patients with congestive failure ever since Withering[1] published his classic monograph. The action of digitalis is not altogether understood yet, and the ideal digitalis preparation possessing the therapeutic virtues of the whole digitalis leaf without its disadvantageous side effects has not been found.

As known, the therapeutic effect of digitalis is due to the action of several glycosides[2-5] contained in the leaves of this plant. Both *Digitalis purpurea* and *Digitalis lanata* contain three glycosides. Stoll[5] demonstrated that lanatosides A and B (*lanata*) are similar to digitoxin and gitoxin (*purpurea*), while gitalin is contained only in the leaves of *purpurea*, and Digoxin only in those of *lanata*.

Gitalin ($C_{35}H_{56}O_{12}$) was isolated by Krafft in 1912[6] and was further studied by Cloetta.[8] Windaus and associates[9] established in 1926 its correct formula and described its behavior on hydrolisis. Gitalin was introduced in clinical practice under the trade name of Verodigen* in 1913 and Straub and Krehl[10] reported on a five-year experience with this drug in 1919. The first clinical use of gitalin in this country was reported by Stroud and associates in 1934.[11] Further clinical studies were done by Baker and Bloom,[12] Levy and Boas,[13] and Batterman and associates.[14-15]

Among the various properties of the digitalis preparations, the following should be considered: (1) rapidity of action; (2) power of accumulation; (3) rapidity of elimination; (4) ratio of therapeutic to toxic dose, and (5) percentage of the drug destroyed in the gastrointestinal tract (ratio of oral to intravenous effective dose).

A comparison of the therapeutic ratios for the various glycosides of *Digitalis purpurea* and *lanata*, as well as for the whole leaves, was made by Batterman and associates.[15,16] Their clinical experience indicates that the powder of digitalis

From the Division of Cardiology of The Chicago Medical School and the Mount Sinai Hospital of Chicago.

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*Verodigen, manufactured by Böhringer and Sons of Mannheim, Germany, contained also a small percentage of by products. (Kiliani[7], Straub and Krehl.[10])

leaves (U.S.P. XII-XIII) and the glycosides of general use have a therapeutic ratio which is between 58 and 66.5 per cent (Table I). This means that the average patient requires about 60 per cent of the toxic dose of the preparation in order to obtain a therapeutic effect. It can be seen that Gitalin (amorphous) possesses a therapeutic ratio of 36.9 with an average increase of 41 per cent in therapeutic range when compared with the other preparations. Therefore, the safety factor for Gitalin (amorphous) seems to be greater than that of any other digitalis preparation.

TABLE I. THERAPEUTIC RATIO DETERMINED BY RAPID ORAL DIGITALIZATION (MULTIPLE DOSE METHOD) FOR VARIOUS DIGITALIS PREPARATIONS (BATTERMAN AND ASSOCIATES)[14-16]

DIGITALIS PREPARATION	THERAPEUTIC RATIO $\left(\frac{\text{Therapeutic Dose}}{\text{Toxic Dose}} \times 100\right)$
Gitalin (amorphous)	36.9
Digitalis leaf (U.S.P. XII-XIII)	66.5
Digitoxin	58.0
Digoxin	60.6

The purpose of our study was: (1) To observe and compare immediate effects of gitalin with similar effects of other purified glycosides. (2) To test tolerance, activity, and stability of the drug, when used intravenously. (3) To investigate summation effect, maintenance dose, and elimination.

MATERIAL AND METHOD OF STUDY

Gitalin is a combination of the aglycone gitaligenin with two molecules of digitoxose. Its behavior on hydrolysis can be represented as follows:

$$\underset{\text{gitalin}}{C_{35}H_{56}O_{12}} + 2H_2O = \underset{\substack{\text{gitoxigenin}\\\text{hydrate}}}{C_{23}H_{36}O_6} + \underset{\text{digitoxose}}{2C_6H_{12}O_4}$$

The glycoside used in our investigation was an aqueous-alcoholic solution of the powder for intravenous use, containing 0.5 mg. of gitalin per c.c.* For comparative studies, Strophanthin K,† lanatoside C,† and digitoxin‡ were used.

Twenty persons were studied. Sixteen were ambulatory patients from the Cardiac Clinic of the Mount Sinai Hospital with a more or less severe congestive failure, while the other four were normal subjects, used for control. None of the sixteen patients had received digitalis for a two-week period prior to intravenous administration of gitalin. Table II shows the etiologic and anatomic diagnoses of the sixteen patients, the type of glycoside used, the total dose administered intravenously, and the number of injections.

*Gitalin (Gitaligin) was supplied by the White Laboratories, Inc.

†Strophanthin K (Strophosid) and lanatoside C (Cedilanid) were obtained through the courtesy of the Sandoz Pharmaceuticals.

‡Digitoxin (Crystodigin) was obtained through the courtesy of Eli Lilly & Company.

Table II. Intravenous Injection of Digitalis Glycosides

No., Name, Age and Sex	Clinical Diagnosis	Drugs Used and Total Dose	No. of Injections
1-GR-33-F	Rheumatic heart disease; mitral insufficiency and stenosis; aortic insufficiency and stenosis; auricular fibrillation	Gitalin 11.5 mg. Lanatoside C 0.8 mg.	9
2-MH-46-M	Arteriosclerotic heart disease; aortic insufficiency and stenosis; myocardial infarct	Gitalin 15 mg. Lanatoside C 0.8 mg. Strophanthin 0.5 mg.	9
3-SB-69-F	Arteriosclerotic heart disease; auricular fibrillation	Gitalin 12.5 mg. Lanatoside C 0.4 mg. Strophanthin 0.25 mg.	9
4-NW-72-M	Arteriosclerotic heart disease; auricular fibrillation	Gitalin 6 mg. Lanatoside C 0.4 mg. Strophanthin 0.25 mg.	3
5-TI-67-M	Arteriosclerotic heart disease; myocardial infarct	Gitalin 3 mg.	1
6-PF-71-M	Arteriosclerotic, hypertensive heart disease; myocardial infarct	Gitalin 18 mg.	4
7-CM-62-M	Arteriosclerotic heart disease; myocardial infarct	Gitalin 6 mg.	2
8-SR-73-F	Arteriosclerotic, hypertensive heart disease	Gitalin 24 mg.	4
9-NF-72-F	Arteriosclerotic heart disease	Gitalin 12 mg.	4
10-HS-65-F	Arteriosclerotic, hypertensive heart disease	Gitalin 12 mg. Lanatoside C 0.4 mg.	5
11-BS-35-M	Rheumatic heart disease; mitral and aortic insufficiency and stenosis; auricular fibrillation	Gitalin 9 mg.	3
12-LA-65-M	Arteriosclerotic heart disease; auricular fibrillation	Gitalin 3 mg. Strophanthin 0.25 mg.	2
13-DM-18-F	Rheumatic heart disease, active; mitral insufficiency and stenosis	Gitalin 4 mg. Digitoxin 0.2 mg.	2
14-FE-50-F	Arteriosclerotic heart disease	Gitalin 4 mg. Digitoxin 0.2 mg. Strophanthin 0.25 mg.	3
15-MA-62-F	Rheumatic and arteriosclerotic heart disease; mitral insufficiency and stenosis	Gitalin 3 mg.	1
16-McGE-58-M	Arteriosclerotic heart disease; myocardial infarct	Gitalin 3 mg.	1
17-FCh-23-M	Normal	Gitalin 4 mg.	1
18-GA-24-M	Normal	Gitalin 4 mg.	1
19-FS-23-M	Normal	Gitalin 4 mg.	1
20-AJ-34-M	Normal	Gitalin 2.5 mg.	1

The following tracings were recorded before injection of the drug: electrocardiogram, including the standard and aV limb leads, and three precordial V leads (V_2, V_4, and V_6, simultaneously taken) in all patients; ballistocardiogram, in ten subjects; electrokymogram of the left ventricular border, in twelve. The apparatus used for recording were: a direct-writing four-channel electrocardiograph, a photoelectric ballistocardiograph, and an electrokymograph.

After the control tracings were taken, the drug was slowly injected in one of the antecubital veins. The corresponding tracings were repeated soon after the injection, and several times later, for a period of at least one hour. In different sessions, the same subjects received intravenous injections of Strophosid 0.25 mg., Cedilanid 0.40 mg., or digitoxin 0.20 mg.

As intravenous administration of gitalin has not been previously studied, the initial dose in the first five patients was 2 mg., or about one-third of the oral digitalizing dose as indicated by Batterman and associates.[14-16] This dose was repeated once every twenty-four hours until full digitalization was reached. Later on, it became clear that an initial dose of from 2.5 to 3 mg. of Gitalin was well tolerated in the average case. Therefore, this amount was injected at the first session in the majority of cases.

A study of the time necessary for elimination of the drug and the optimal maintenance dose by intravenous injection was made in selected cases with the electrocardiographic method described by Gold and associates[17-20] and used by several other investigators. This method is based on the immediate changes of the S-T segment and of the T wave, caused by digitalis in certain patients. The injections were repeated at intervals which varied from twenty-four hours to seven days.

A complete evaluation of the results was obtained by correlating the changes of the electrocardiographic, electrokymographic, and ballistocardiographic tracings with the clinical observations. The present report is concerned mainly with clinical data and changes of the electrocardiogram, while a second paper will consider the changes of the ballistocardiogram and electrokymogram. Besides the RS-T segment and the T-wave changes, the alterations of the electrical systole were also studied. This was done by comparing the Q-T intervals, corrected according to Taran and Szilagyi,[25] in the tracings taken before and after injection of gitalin (Table III).

RESULTS

Full digitalizing dose by means of intravenous gitalin was found to be between 5 and 6 mg. The drug was extremely well tolerated in every case. No ectopic rhythms were noted following the injections. Nausea, vomiting, diarrhea, tired feeling, or oppression were not presented by the patients. The complete lack of side effects is especially indicated by the behavior of two patients who had previously shown unpleasant reactions to other digitalis preparations while, at the same time, their congestive failure was not relieved.

TABLE III. ELECTROCARDIOGRAPHIC

NO., NAME, AGE AND SEX	CLINICAL DIAGNOSIS	AMOUNT OF GITALIN INJECTED (MG.)	CHANGE OF RATE: AVERAGE INCREASE OR DECREASE (%)	
			IMMEDIATELY AFTER INJECTION (%)	ONE HOUR AFTER INJECTION (%)
1-GR-33-F	Rheumatic heart disease; mitral and aortic insufficiency and stenosis; auricular fibrillation	3 2.5	−10 +10	−20 Control values
2-MH-46-M	Arteriosclerotic heart disease; aortic insufficiency and stenosis; myocardial infarct	5 2.5	None None	−10 None
3-SB-69-F	Arteriosclerotic heart disease; auricular fibrillation	2.5	−10	−10
4-NW-72-M	Arteriosclerotic heart disease; aortic insufficiency and stenosis; auricular fibrillation	2.5	−20	−20
5-TJ-67-M	Arteriosclerotic heart disease; myocardial infarct	3	−10	Control values
6-PF-71-M	Arteriosclerotic, hypertensive heart disease; myocardial infarct	4 6	−10 None	−10 −10
7-CM-62-M	Arteriosclerotic heart disease; myocardial infarct	4	None	None
8-SR-73-F	Arteriosclerotic, hypertensive heart disease	4 3	None −10	None Control values
9-NF-72-F	Arteriosclerotic heart disease	3 3	None −10	None −10
10-HS-65-F	Arteriosclerotic, hypertensive heart disease	5 3	None None	−10 −10
11-BS-35-M	Rheumatic heart disease; mitral and aortic insufficiency and stenosis; auricular fibrillation	3 3	−10 −10	−10 −10
12-LA-65-M	Arteriosclerotic heart disease; auricular fibrillation	3	None	+10

CASE 1.—B.S. was a 31-year-old white man with a history of rheumatic fever at the age of 17. He first came to the Cardiac Clinic of Mount Sinai Hospital in July, 1948, because of severe exertional dyspnea, orthopnea, pain in the right upper quadrant of the abdomen increased by exertion, and edema of the legs. The diagnosis then was: rheumatic heart disease with mitral stenosis and regurgitation and aortic regurgitation; auricular fibrillation; congestive failure. From July, 1948, to March, 1951, the patient received digitalis powder or tincture, digitoxin, and Digoxin. To each of these preparations, the patient reacted with nausea, vomiting, and diarrhea so that treatment was repeatedly interrupted. Mercurial diuretics were well tolerated. When the patient first came to our laboratory, there was auricular fibrillation with rapid ventricular rate, markedly enlarged liver, and edema of both legs. Three mg. of gitalin was injected intravenously the first day, and a similar dose was given forty-eight hours later. Then the patient was put on a daily maintenance dose of 0.5 mg. of gitalin by mouth. A marked clinical improvement was noted shortly after the second injection; after two weeks, all the signs of congestive failure had disappeared. From March, 1951, to the present day the patient has continued on a daily maintenance dose of 0.5 mg. gitalin by mouth, and has been able to work as clerk in a bookstore without discomfort. His heart rate has decreased from an average of 120 to an average of 60; there still is auricular fibrillation and the electrocardiogram shows evidence of digitalis effect.

CHANGES CAUSED BY GITALIN

S-T CHANGES		POLARITY CHANGES		Q T C		
IMMEDIATELY AFTER INJECTION	ONE HOUR AFTER INJECTION	IMMEDIATELY AFTER INJECTION	ONE HOUR AFTER INJECTION	CONTROL	IMMEDIATELY AFTER INJECTION	ONE HOUR AFTER INJECTION
Yes	Yes	Yes	Yes	0.413	0.361	0.436
Yes	Yes	Yes	Yes	0.444	0.407	0.369
No	No	No	Yes	0.389	0.371	0.400
No	No	No	Yes	0.400	0.363	0.388
No	Yes	No	Yes	0.400	0.490	0.408
Yes	Yes	Yes	Yes	0.467	0.416	0.416
No	Yes	Yes	Yes	0.415	0.403	0.401
No	Yes	Yes	Yes	0.422	0.404	0.404
No	No	Yes	Yes	0.408	0.392	0.392
Yes	Yes	Yes	Yes	0.413	0.381	0.381
No	No	No	Yes	0.436	0.417	0.417
No	Yes	Yes	Yes	0.459	0.453	0.443
No	Yes	No	Yes	0.478	0.478	0.485
No	Yes	No	Yes	0.436	0.471	0.478
No	Yes	No	Yes	0.408	0.427	0.417
No	Yes	No	Yes	0.422	0.417	0.417
Yes	Yes	Yes	Yes	0.436	0.413	0.408
Yes	Yes	Yes	Yes	0.406	0.369	0.369
No	Yes	No	Yes	0.485	0.461	0.417

CASE 2.—G.R. was a 33-year-old Negro woman with history of rheumatic fever at the age of 14. First admission to Mount Sinai Hospital was in October, 1950, because of fever, malaise, and dependent edema. Diagnosis of rheumatic heart disease and subacute bacterial endocarditis was made; penicillin treatment was instituted. After seven weeks, the patient was transferred to University of Illinois Hospital for further treatment and was discharged after five months, apparently cured.

Second admission to Mount Sinai was in July, 1951, because of exertional and nocturnal dyspnea, swelling of the abdomen, and dependent edema. The diagnosis was: rheumatic heart disease; mitral stenosis and regurgitation and aortic regurgitation, and congestive heart failure. The patient was alternately treated with digitoxin, Scillaren, and Cedilanid, plus quinidine, and Mercuhydrin. Nausea and vomiting made it necessary to change the digitalis preparation several times, but the patient was not relieved. After ten weeks, the patient was discharged in an improved condition. However, in spite of treatment, some degree of congestive failure was still present and frequent ventricular premature contractions were noted.

When the patient first came to the laboratory in September, 1951, she exhibited evidence of severe congestive failure, such as extreme shortness of breath, dependent edema, abdominal distention, and right hydrothorax. The electrocardiogram showed sinus rhythm; there were frequent

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ventricular premature contractions; the average heart rate was 110. Intravenous gitalin therapy was started but it soon became advisable to hospitalize the patient. Therefore, she was admitted to Mount Sinai Hospital in November. There she was treated with gitalin, 2.5 mg. every 48 hours intravenously, and 2 c.c. of Mercuhydrin intramuscularly twice a week. After four weeks of therapy, the patient had markedly improved. She was then placed on oral Scillaren and Mercuhydrin, and discharged.

Four weeks later, when the patient came to the Cardiac Clinic, her condition had severely deteriorated: in spite of evidence of cardiac failure, nausea was present and ventricular premature contractions were frequent. The patient was placed on oral gitalin. Since then, she has been checked monthly. She has been in good general condition and has been able to take up housework for the first time in three years. The heart rate is stabilized around 80 and there are only occasional premature contractions.

Mention should be made that another patient with rheumatic and arteriosclerotic heart disease, auricular fibrillation, and rapid ventricular rate (130 average) developed paroxysmal pulmonary edema within thirty minutes from an intravenous injection of 2.5 mg. of gitalin. The pulmonary edema subsided in the following twelve hours.

Electrocardiographic Changes.—Differentiation should be made between effect of an initial dose and after full digitalization. None of the glycosides used in our study was injected in full digitalizing dose in the first session.

Immediate Changes.—Marked changes appeared in the electrocardiogram (as well as in the ballistocardiogram and electrokymogram) within twenty minutes from the intravenous injection of gitalin. These changes were similar to those observed by others[26-33] and by us after injection of other cardiac glycosides.

Heart Rate.—Soon after the injection, the heart rate changed slightly in eight out of sixteen cases. In four there was a decrease, while the other four showed either decrease or increase in different sessions. One hour after injection, no change from control values was noted in six cases; a decrease, in five; an increase in one. The other four cases exhibited different behavior following the various injections. In one patient with auricular fibrillation and slow ventricular rate plus occasional ventricular standstills, the average ventricular rate increased from 60 to 70 and the rhythm became more regular after each injection. Only one patient developed bigeminal rhythm after each gitalin injection; however, the arrhythmia disappeared each time within an hour. Bigeminy also developed after injection of either Cedilanid or digitoxin and lasted longer. A marked drop in heart rate (from 15 per cent to 50 per cent) occurred in all but one case twenty-four hours after full digitalization. While this was true both for cases with sinus rhythm and with auricular fibrillation, the most remarkable decrease was noted in cases with auricular fibrillation and rapid ventricular rate. Negligible differences were noted between the changes of heart rate occurring within one hour from an injection of gitalin and those following injection of lanatoside C, digitoxin, or strophanthin. A persistent low ventricular rate was generally present twenty-four hours after full digitalization with gitalin, lanatoside C, or digitoxin. On the contrary, the rate returned to previous level twenty-four hours after injection of strophanthin.

Electrical Systole.—The duration of electrical systole was measured in twelve patients. Following injection of gitalin, the corrected Q-T presented an immediate average decrease of about 10 per cent in seven cases (Table III); on the

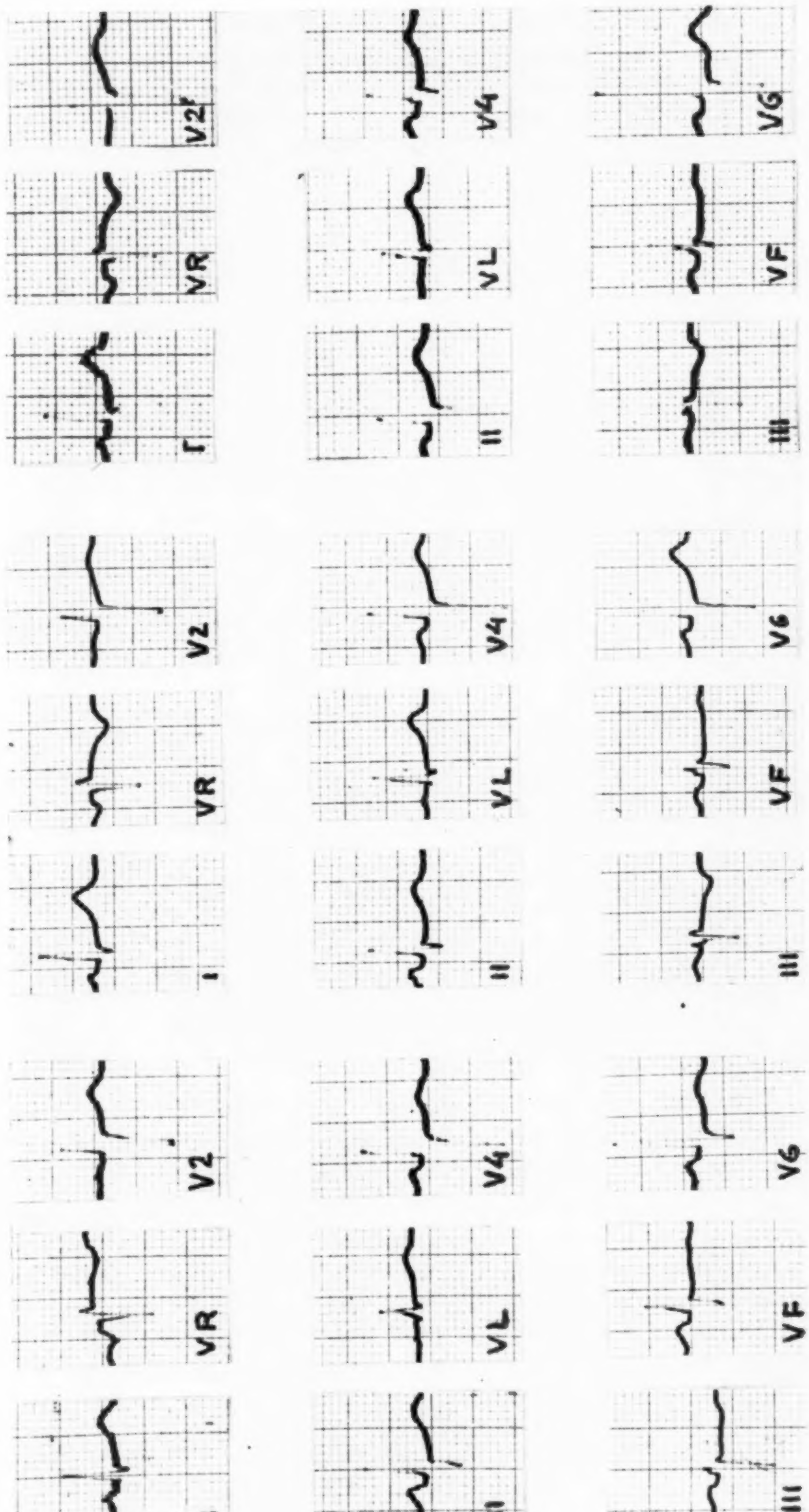
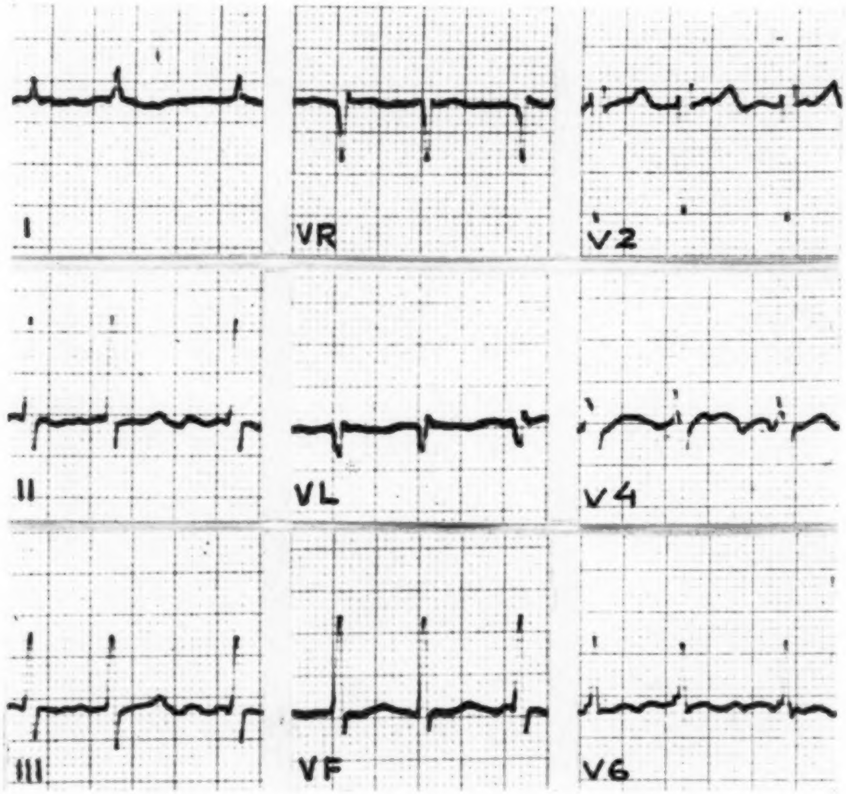


Fig. 1.—Electrocardiogram of a 65-year-old woman with sinus rhythm showing effect of gitalin. *A*, Before injection. *B*, Soon after intravenous injection of 4 mg. of gitalin. *C*, One hour later.

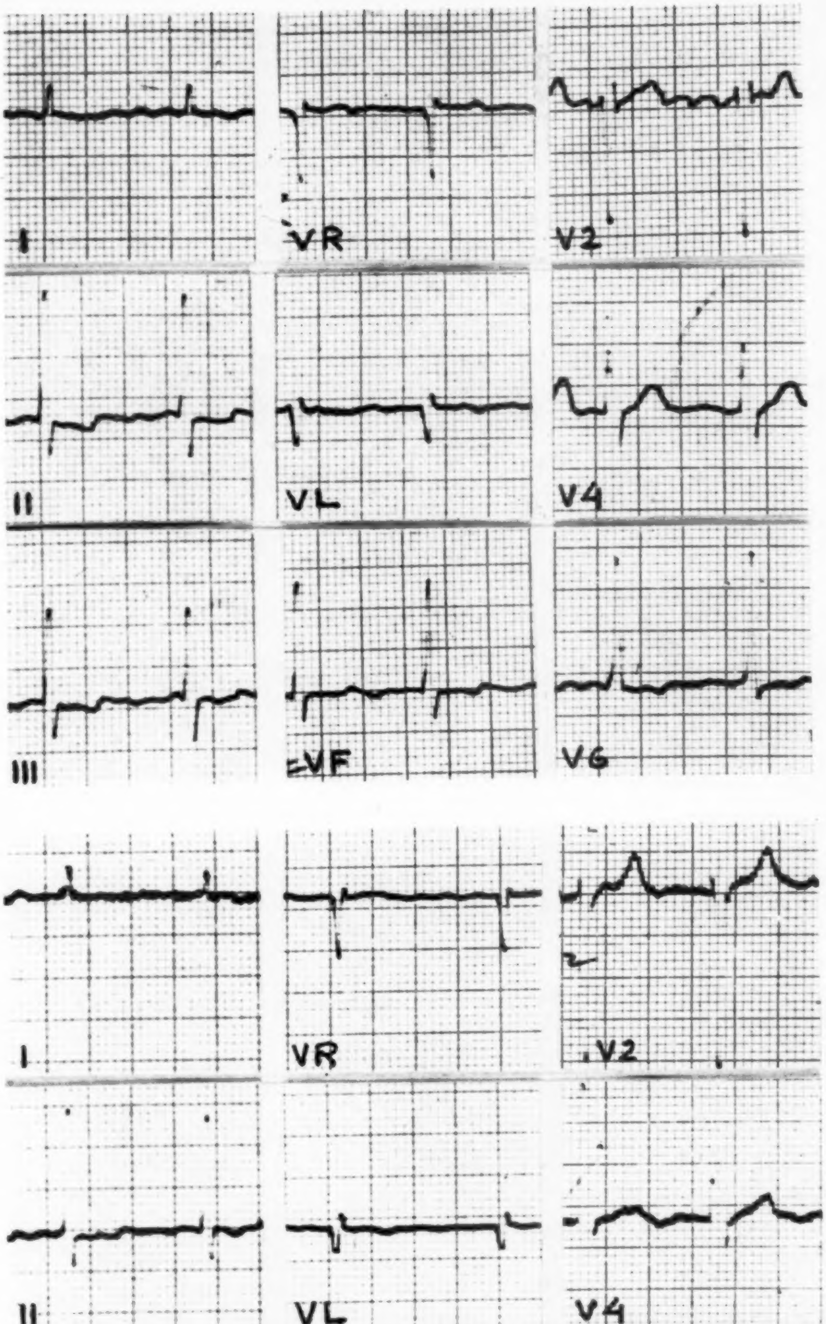
contrary, there was a slight increase of Q-T in two cases, and various behavior after different injections in the others. One hour after injection, five subjects showed a decrease of the corrected Q-T interval; three, a slight increase. Two other patients had a slight increase one hour after the first injection; a decrease, after the second injection, administered the following day. Twenty-four hours after digitalization, the corrected Q-T was reduced in every instance where a tracing was taken. Similar results were obtained with lanatoside C and digitoxin, while the Q-T interval had returned to normal twenty-four hours after injection of strophanthin.



A.

Fig. 2.—Electrocardiogram of a 35-year-old man with auricular fibrillation showing effect of gitalin. A, Before injection. B, Soon after intravenous injection of 3 mg. of gitalin. C, One hour later.

S-T and T Changes.—A change of polarity of the T wave after injection of gitalin took place immediately in three cases and within one hour from the injection, in eight others. A depression of the RS-T segment of more than 0.5 mm. in Leads I, II, aV_L and V_6, appeared within an hour in twelve cases out of sixteen. The T-wave inversion caused by gitalin lasted from three to four days after one single dose of 3 mg. of gitalin. T-wave inversion due to a single dose of strophanthin had disappeared within twenty-four hours. On the contrary, the inversion of the T wave caused by a single injection of lanatoside C disappeared from four to five days after the injection, and that caused by digitoxin, from five to seven days.



B.

C.

Fig. 2, *B* and *C*.—(*For legend see opposite page.*)

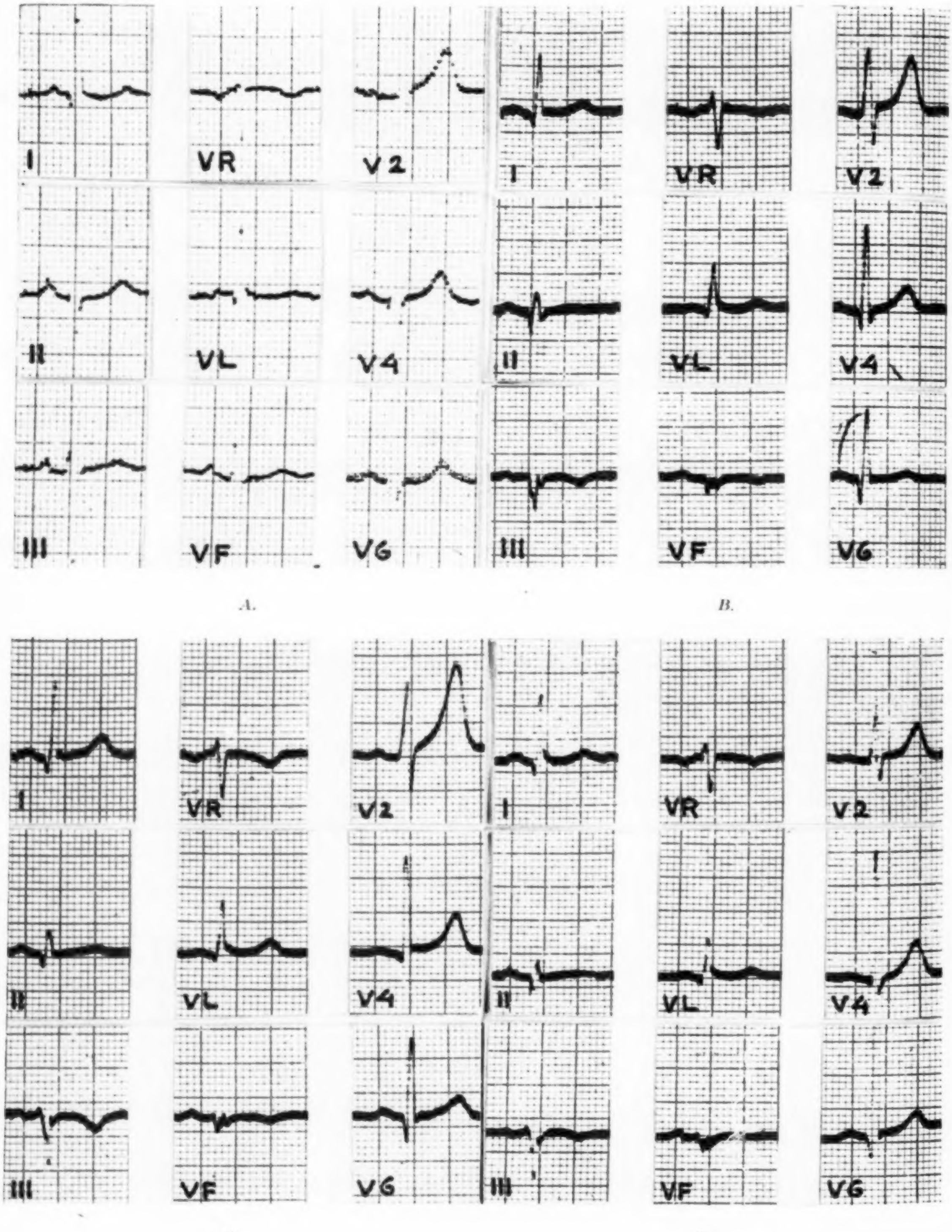


Fig. 3.—Electrocardiogram of a 46-year-old man with sinus rhythm showing the effects of gitalin, strophanthin, and digitoxin. *A*, Before injection. *B*, Soon after intravenous injection of 3 mg. of gitalin. *C*, Soon after intravenous injection of 0,25 mg. of strophanthin. *D*, Soon after intravenous injection of 0.2 mg. of digitoxin.

DISCUSSION

Four glycosides have been isolated from the leaves of the two main plants of the digitalis type (*Digitalis purpurea* and *Digitalis lanata*). Two of these glycosides are present in both while the other two are respectively present in only one of the two plants. Gitalin is the glycoside present only in *Digitalis purpurea*.

In the search for the ideal digitalis preparation, gitalin, though not new, was largely overlooked until recently. Clinical reports indicating that the margin between therapeutic and toxic doses (therapeutic ratio) is much wider than for other digitalis preparations, and have focused the attention on gitalin. The present study was mainly concerned with clinical and electrocardiographic observations.

Gitalin was administered by the intravenous route in four normal subjects and in sixteen ambulatory patients. Comparison was made with the effects of Strophanthin K, lanatoside C, and digitoxin, also given by vein, in the same subjects after a suitable interval.

Clinical experience showed that an initial dose of 2.5 to 3 mg. is well tolerated and that full digitalization is obtained by giving two such injections at twenty-four hours' interval. As this coincides with the oral digitalizing dose found by Batterman and associates,[14-15] attention should be drawn to the effect that only minimal amounts of the drug are inactivated by the enzymes of the gastrointestinal tract.

Administration of the drug was always well tolerated. In particular two patients with congestive failure who tolerated poorly other glycosides had excellent results with intravenous gitalin and have been kept in good condition for several months since the switch to gitalin. These observations confirm Batterman's contention that the therapeutic ratio of gitalin is higher than that of other glycosides.[14-16]

The changes of the heart rate due to gitalin are similar to those caused by other digitalis glycosides. They were particularly apparent twenty-four hours after full digitalization and especially in patients in failure with auricular fibrillation and rapid ventricular rate.

The decrease of the Q-T interval reveals a typical digitalis effect[21-24] of gitalin, as do the depression of S-T and the inversion of the T wave. The electrocardiogram, therefore, fails to reveal significant differences between gitalin and other digitalis glycosides.

The persistance of the S-T and T changes has been studied, according to the method of Gold and associates,[17-19] in order to evaluate the elimination of gitalin. It was noted that the T wave returned to normal within twenty-four hours after strophanthin; within three to four days after gitalin; within four to five days after lanatoside C; within five to seven days after digitoxin. This indicates a rapid elimination of gitalin which apparently should be placed between strophanthin and lanatoside C, although nearer to the latter. Therefore, a successful intravenous maintenance therapy can be attained only if the injections are given at an interval of seventy-two to ninety-six hours, or about two every week.

In conclusion, gitalin proved to be a powerful and safe digitalis preparation which is as effective by intravenous injection as by mouth and which is rapidly

eliminated. Intravenous gitalin can be given biweekly in doses of 2.5 mg., or can be used for rapid initiation of therapy, following which digitalization can be continued by the oral route.

The wide margin of safety of the drug and the relative lack of side effects seem to indicate gitalin as the drug of choice in patients with congestive failure due to rheumatic carditis or coronary heart disease, and in patients with cardiac failure exhibiting evidence of hyperexcitability of the myocardium (ectopic rhythms). On the other hand, ambulatory patients on maintenance dose of gitalin should be checked at frequent intervals because the rapid elimination of the drug may lower the blood level of digitalis to below effective figures.

SUMMARY

Intravenous administration of gitalin, a glycoside of *Digitalis purpurea*, was studied in sixteen ambulatory patients with various degrees of congestive failure, and in four control subjects. Clinical and electrocardiographic observations are reported. Comparison with strophanthin, lanatoside C, and digitoxin was made.

Initial intravenous dose was found to be between 2.5 and 3 mg.; total digitalizing dose, from 5 to 6 mg. Two injections at twenty-four hour intervals were sufficient to digitalize the average ambulatory patient. Maintenance was obtained with two weekly injections of 2.5 mg. Administration of the drug caused no appreciable side effects. Two difficult clinical cases who tolerated poorly other glycosides showed good tolerance toward gitalin and obtained beneficial results from its use.

The changes of the heart rate, of the Q-T interval, of the S-T interval, and of the T wave caused by gitalin are similar to those due to other digitalis glycosides. Persistance of S-T and T-wave changes were utilized for a comparative study between the various glycosides. This revealed that gitalin is eliminated within three to four days and that its rapidity of elimination is between that of strophanthin and that of lanatoside C, although nearer to the latter.

The wide margin of safety, the relative lack of side effects, and the rapid elimination indicate gitalin as the drug of choice in cardiac failure caused by rheumatic carditis or coronary heart disease, and in cases with ectopic ventricular rhythms. Ambulatory patients need frequent checking on account of the rapid elimination of the drug.

REFERENCES

1. Withering, W.: An Account of the Foxglove and Some of Its Medical Uses: With Practical Remarks on Dropsy and Other Diseases, 1785, Birmingham and London. M. Swinney, Publisher.
2. Gottlieb, R., and Magnus, R.: Ueber die Gefaesswirkung der Koerper der Digitalisgruppe, Arch. f. exper. Path. u. Pharmakol. **47**:135, 1902.
3. Weese, H.: Digitalis, Leipzig, 1936, Georg Theime.
4. Wenckebach, K. F.: Discussion on the Effect of Digitalis on the Human Heart, Brit. M. J. **2**:1600, 1910.
5. Stoll, A.: The Cardiac Glycosides, London, 1937, The Pharmaceutical Press.
6. Krafft, F.: Die Glykoside der Blaetter der Digitalis purpurea, Arch. d. Pharm. **250**:118, 1912.
7. Kiliani, H.: Ueber Digitoxin und Gitalin, Arch. d. Pharm. **251**:562, 1913.

8. Cloetta, M.: Die Darstellung und chemische Zusammensetzung der aktiven Substanzen Digitalisblaetter, etc., Arch. f. exper. Path. u. Pharmakol. **112**:261, 1926.
9. Windaus, A., Westphal, K., and Stein, G.: Neue Abbauprodukte des Digitogenin, etc. Ztschr. f. Physiol. Chem. **151**:86, 1926.
10. Straub, W., and Krehl, L.: Ueber Verodigen (Gitalin), Deutsche med. Wchnschr. **45**:11, 1919.
11. Stroud, W. D., Livingston, A. E., Bromer, A. W., Van der Veer, J. B., and Griffith, G. C.: The Use of Verodigen (a Digitalis Glycoside) in Cardiovascular Disease, Its Biological Assay, and Pharmacological Action, Ann. Int. Med. **8**:710, 1934.
12. Baker, J. P., Jr., and Bloom, N.: Clinical Studies on Verodigen, a Digitalis Glycoside, Ann. Int. Med. **10**:605, 1936.
13. Levy, H., and Boas, E. P.: Clinical Studies of Gitalin and of Digitalis in the Treatment of Auricular Fibrillation, AM. HEART J. **15**:643, 1938.
14. Batterman, R. C., and De Graff, A. C.: Comparative Study on the Use of the Purified Digitalis Glycosides: Digoxin, Digitoxin and Lanatoside C, for the Management of Ambulatory Patients With Congestive Heart Failure, AM. HEART J. **34**:663, 1947.
15. Batterman, R. C., De Graff, A. C., Gutner, L. B., Rose, A. O., and Lhowe, J.: Studies With Gitalin (Amorphous) for the Treatment of Patients With Congestive Heart Failure, AM. HEART J. **42**:292, 1951.
16. Batterman, R. C., De Graff, A. C., and Rose, A. O.: The Therapeutic Range of Gitalin (Amorphous) Compared With Other Digitalis Preparations, Circulation **5**:201, 1952.
17. Gold, H., Cattell, McK., Modell, W., Kwit, N. T., and Kramer, M. L.: A Comparison of the Speed, the Intensity and the Duration of Action of Four Digitalis Glycosides by Intravenous Injection in Man, Proc. Fed. Am. Soc. Exp. Biol. **2**:80, 1943.
18. Gold, H., Cattell, McK., Otto, H. L., Kwitt, N. T., and Kramer, M. L.: A Method for the Bioassay of Digitalis in Humans, J. Pharmacol. & Exper. Therap. **75**:196, 1942.
19. Gold, H., Cattell, McK., Modell, W., Kwit, N. T., Kramer, M. L., and Zahm, W.: Clinical Studies of Digitoxin, J. Pharmacol. & Exper. Therap. **32**:1807, 1944.
20. Levine, H., Nahum, L. H., Geller, H. M., and Sikand, R. S.: Genesis of the Electrocardiographic Pattern of Digitalis, Am. J. Phyiol. **167**:726, 1951.
21. Tandowsky, R. M., Anderson, N., and Vandeventer, J. K.: An Electrocardiographic and Clinical Study of Various So-called Cardiac Drugs, AM. HEART J. **28**:298, 1944.
22. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, J. Exper. Med. **21**:593, 1915.
23. Pardee, H. E. B.: Clinical Observations on the Use of Intravenous Digitalis Preparations, J. A. M. A. **91**:147, 1928.
24. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, AM. HEART J. **10**:546, 1935.
25. Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole in Acute Rheumatic Carditis in Children, AM. HEART J. **33**:14, 1947.
26. Liljenstrand, Ake: Digitoxin Intoxication in a Woman With Normal Heart, Cardiologia **15**:537, 1949-1950.

THE RELATION OF THE CHOLINE CYCLE TO CARDIAC DECOMPENSATION: ACETYLCHOLINE METABOLISM IN THE DOG HEART-LUNG PREPARATION

WM. M. GOVIER, M.D., W. A. FREYBURGER, PH.D., ANNA J. GIBBONS, B.S., BENNETT G. HOWES, AND ERVINS SMITS

KALAMAZOO, MICH.

ALTHOUGH many effects of cardiac glycosides have been demonstrated,[1] the relationship between these and the therapeutic action of the glycosides has apparently been elusive. In most cases the demonstration of an impaired biochemical function in congestive heart failure which is returned toward the normal state by digitalis is lacking.

It is known (Harrison and associates[2]) that a reduction in muscle potassium accompanies congestive failure in human beings. Many workers have pointed out (Calhoun and Harrison,[3] Cattell and Goodell,[4] Wood and Moe,[5] Mangun and Myers,[6] Boyer and Poindexter,[7] and others) that therapeutic doses of digitalis produce a retention in the cell or a return to the cell of potassium, whereas toxic doses produce a further loss of intracellular potassium. This phenomenon of loss of K^+ in muscle fatigue has been observed in skeletal muscle by Calhoun and associates,[8] Fenn and associates,[9] and Tipton,[10] and in the muscle of adrenal insufficiency by Zwemer and Truszkowski,[11] and others. Since digitalis can effect a return of potassium to the cell, it is not too surprising that Zwemer and Loewenstein[12] found digitalis glycosides to lower the elevated plasma potassium and prolonged life in adrenalectomized animals.

The recent work of Greig and associates[13] has clarified the mechanism of increased cell permeability. These workers have demonstrated that permeability of red blood cells to potassium is regulated by the integrity of the cholinesterase-acetylcholine system. Lack of substrate or inhibition of the esterase increases the permeability with loss of potassium.

It occurred to the authors that the results of Greig and associates might be applied to the problem of congestive failure, and that determination of cholinesterase activity in heart muscle before and during failure, and after therapy, might be illuminating.

The present communication is not intended as a complete work. It is hoped that it may stimulate other investigators to consider the hypothesis presented herein so that it may be either affirmed or negated.

From the Research Division, The Upjohn Company, Department of Pharmacology, Kalamazoo, Mich.

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METHODS

Heart-lung preparations were set up in the classical manner; the dogs were previously anesthetized with either pentobarbital or thiopental sodium. Large animals were used in order to provide hearts of a size suitable for biopsy. Most of these preparations were preliminarily atropinized by the injection of 5 mg. of atropine sulfate into the venous reservoir. The rationale for this procedure will be explained in the next section. Vagus and phrenic nerves were ablated. A sample of heart muscle was removed by biopsy of the left ventricle within two minutes after previous ligation of coronary supply to the desired area. The defect

TABLE I. PENTOBARBITAL FAILURE
(γ ESTER DESTROYED PER MG. DRY WEIGHT PER HOUR)

EXP. NO.	CONTROL SAMPLE	AT FAILURE	AFTER OUABAIN	ANESTHESIA	METHOD	ASSAY SUBSTRATE	ATROPINE SULFATE
2016-13	15.1	13.0	13.6	PB	Mano.	AcCh	—
2016-16	13.5	14.9	15.0	PB	Mano.	AcCh	—
2016-78	12.6	9.7	11.7	PB	Mano.	AcCh	—
2055-12	18.1	15.3	19.3	PB	Mano.	AcCh	—
2131-4	17.1	15.1	15.4	PB	Mano.	AcCh	+
2131-10	21.8	15.7	19.4	PB	Mano.	BzCh	+
2131-13	18.5	14.4	15.1	PB	Mano.	BzCh	+
2131-17	13.1	17.6	16.3	PB	Mano.	BzCh	+
2131-37	33.0	25.9	15.3	PB	Color.	BzCh	+
2131-39	84.4	74.0	93.1	PT	Mano.	BzCh	+
2131-40	169.0	128.0	150.0	PT	Mano.	BzCh	+
2131-41	108.0	11.8	120.0	PT	Mano.	BzCh	+
CONTROLS (NO OUABAIN)							
2131-61	110.0	95.0	18.2	PT	Color.	BzCh	+
2131-62	68.6	85.7	16.9	PT	Color.	BzCh	+
2131-66	87.8	64.4	116.2	PT	Color.	BzCh	+
2131-67	70.5	101.0	77.2	PT	Color.	BzCh	+
2131-72	65.3	105.3	57.5	PT	Color.	BzCh	+
2131-73	174.0	146.0	52.8	PT	Color.	BzCh	+
2131-74	55.4	144.8	68.4	PT	Color.	BzCh	+
2131-75	72.2	120.0	88.9	PT	Color.	BzCh	+
2131-77	52.0	65.0	41.3	PT	Color.	BzCh	+
2131-64	63.0	12.4		PT	Color.	BzCh	+
2131-7	30.8	21.9		PB	Mano.	BzCh	+
2131-141	108.5	82.5		PT	Color.	BzCh	+
2131-143	113.0	35.4		PT	Color.	BzCh	+
2131-145	165.2	169.4		PT	Color.	BzCh	+

PB = Pentobarbital-sodium
PT = Pentothal sodium (the trademark applied by Abbott Laboratories to thiopental sodium)
BzCh = Benzoylcholine
AcCh = Acetylcholine

was closed by interrupted sutures. After failure of the heart by the administration of 65 to 260 mg. of pentobarbital sodium, 60 to 120 mg. of physostigmine, alkaloid, 1 to 2 Gm. of penicillin G, or 5 to 30 mg. of diisopropyl fluorophosphate, a second similar biopsy was taken and the preparation given appropriate amounts of a compound having positive inotropic activity. In all experiments, control and treated, a third biopsy sample was removed fifteen to twenty minutes after the second.

The cholinesterase of dog heart muscle was characterized according to Augustinsson[14] (that is, by offering acetyl-betamethylcholine and benzoylcholine as substrates to the muscle homogenate) and was found to be almost entirely of the pseudo or nonspecific type.

Cholinesterase activity was determined either manometrically on the homogenates of the iced biopsy samples by the method of DuBois and Mangun[15] or colorimetrically by the method of Hestrin,[16] using calcium-free Ringer 1-bicarbonate and benzoylcholine or acetylcholine as substrate in final concentration of 0.015M. Results are expressed in the tables to follow as γ substrate destroyed per mg. dry weight per hour.

It will be noted in Table I that the colorimetric method gives in general higher values than the manometric method. This is due, at least in part, to the fact that both autohydrolysis blanks and basal CO_2 production blanks were subtracted in the case of the manometric determinations, whereas the latter blank obviously was not subtracted in the case of the colorimetric estimations.

RESULTS AND DISCUSSION

I. *The Choline Cycle.*—The mode of energy supply for continued integrity of cell membranes according to Greig and Holland[13] can be shown simply by the skeleton diagram presented in Fig. 1.

$$\text{acetyl} + \text{choline} \xrightarrow[\text{acetylase (co A) + energy}]{\text{choline}} \text{acetylcholine}$$

$$\text{acetylcholine} \xrightarrow{\text{cholinesterase}} \text{choline} + \text{acetyl and energy}$$

$$\text{choline} + \text{acetyl and energy} \longrightarrow \text{maintenance of cell wall integrity}$$

Fig. 1.

This diagram is amplified in Fig. 2 to clarify more of the enzymically catalyzed reactions to be considered later.

1. acetyl ∼ Co A-protein I + choline-protein II ——→ Co A + protein I + acetylcholine-protein II
2. Acetylcholine-protein II ——→ acetylcholine + protein II
3. Acetylcholine $\xrightarrow[\text{esterase}]{}$ choline + acetyl

Fig. 2.

Equation 1 is an adaptation of that of Stadtman and associates[17] who have shown Coenzyme A to be implicated in all acetylation mechanisms so far determined. In this schema protein I is the transacetylase; protein II, the acceptor enzyme. It is also generally accepted that acetylcholine is synthesized as a protein complex (Mann, Tenenbaum, and Quastel[18]) which breaks into a protein and

acetylcholine under various conditions. This reaction may be nonenzymically catalyzed. It would seem reasonable to suppose that the protein of Mann and associates[18] may be the acceptor enzyme of Stadtman and associates[17] as was suggested by Mann, Tenenbaum, and Quastel.[19] Reaction 3 is the well-known one catalyzed by cholinesterase.

In this communication it should be borne in mind that the acetylcholine used for the preservation of cell membrane integrity is in all probability not freely diffusible so as to produce widespread pharmacologic effects, or it is synthesized in such proximity to the esterase that it is rapidly metabolized before it has time for such diffusion. This concept may help to bridge the gap between the notion of acetylcholine as a violent pharmacologic agent when injected and the concept presented by Greig and associates[13] of acetylcholine as a normal metabolite necessary for cell integrity.

It should also be noted that the ester linkage of acetylcholine is not rich in energy. It is perhaps useful to think of the function of acetylcholine in the preservation of cell membrane integrity as a transfer of chemical energy to mechanical energy, that is, (ATP → pyrophosphorylcoenzyme A → acetylcoenzyme A → acetylcholine) with acetylcholine serving as an ion-exchanger as suggested by Bergmann[20] and Frommel and associates.[21]

As previously mentioned, atropine was administered to most of the heart-lung preparations. This was done in order to block actions of choline and choline derivatives on effector sites, thus reducing the incidence of pulmonary edema and cardiac irregularities without diminishing beneficial cardiac effects. In the absence of atropine, physostigmine elicited a primary pulmonary edema which resulted in early deterioration of the preparation. Atropine had no effect on the pseudocholinesterase of dog heart muscle in vitro in concentrations of 1.33 to 8.0×10^{-9} molar.

The normal range of cholinesterase in dog hearts was established in the following manner. Nine dogs were killed immediately after anesthetization with Pentothal sodium and a sample of muscle removed from the left ventricle of each. These samples were analyzed by the colorimetric method. The values obtained in γ benzoylcholine destroyed per mg. dry muscle per hour are as follows: 190, 191, 152, 200, 169, 223, 222, 155, 116, with an average of 180. As will be seen when these values are compared with the colorimetrically analyzed initial biopsy values in the heart-lung preparations, the operative procedures involved in setting up the heart-lung preparation result in a marked decrease in esterase activity.

In order to determine the spread to be expected among several values taken from the same left ventricle, three animals were killed and two or three samples taken from the left ventricle of each. The results are tabulated as follows:

Sample	1	2	3
Dog 1	211	193	261
Dog 2	119	143	85
Dog 3	146	163	

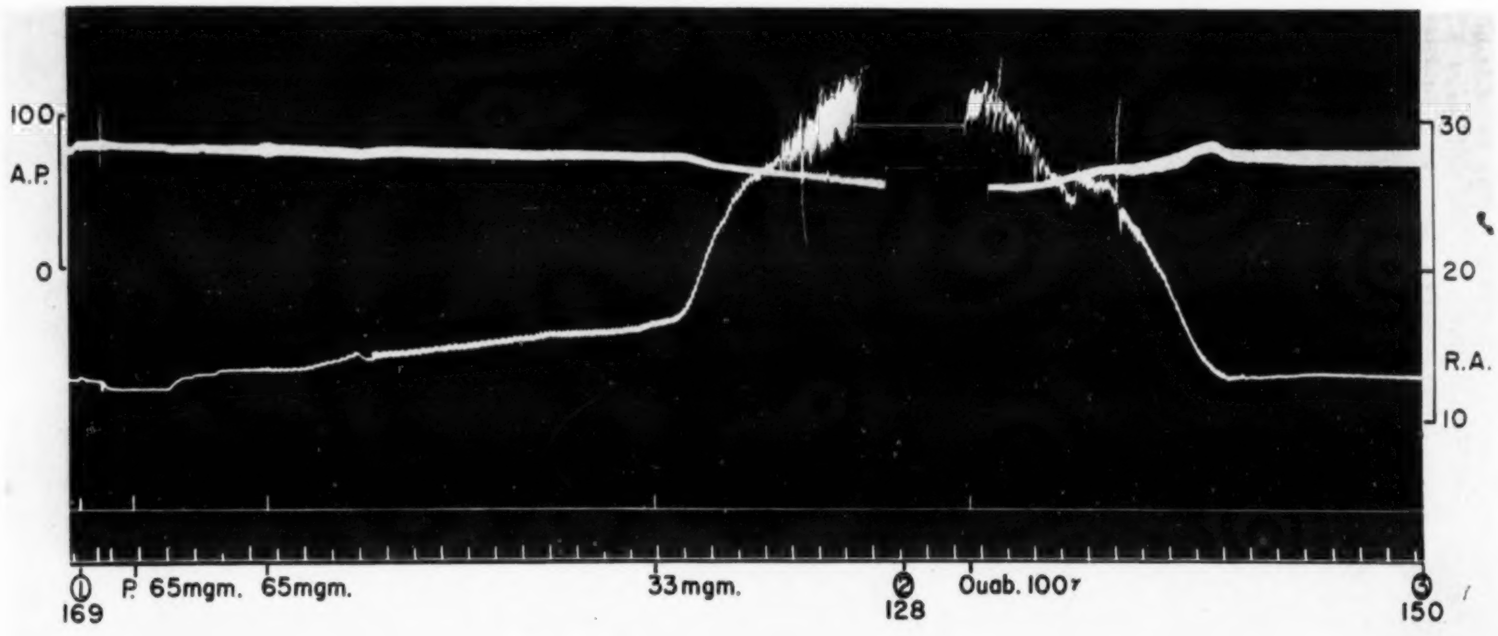

Fig. 3.—Heart-lung Preparation. Dog, male, 18.0 kilograms. Thiopental sodium 20 mg./kg. Atropine sulfate 5.0 mg. Recording from the top: Arterial pressure mm. Hg; right auricular pressure cm. H_2O; signal; time in minutes. *(1) (2) (3)*, Cholinesterase activity of biopsy samples. *P*, Pentobarbital sodium. *Ouab.*, ouabain.

It cannot be denied that the variation is considerable, but this is probably not important since one must assume that the values follow the normal statistical distribution in sampling. A consistent rise or fall during failure or recovery would be significantly different than the normal sampling distribution.

II. *The Effects of Compounds Influencing the Choline Cycle.*—

A. *Pentobarbital.*—Pentobarbital has been employed by many investigators to produce decompensation in the heart-lung preparation. Table I demonstrates a fall in cholinesterase activity in failure produced by pentobarbital in seventeen of twenty-six experiments. Although this is not statistically significant, we believe that the decrease in esterase in failure is valid. This point will be discussed later in this section. Fig. 3 shows a tracing illustrating the usual course of events in this type of experiment.

When the effect of ouabain is considered, it is seen in Table I that in ten of twelve experiments ouabain administration was followed by no change or an increase in esterase activity. In the control series eight of nine experiments showed a marked fall in esterase activity as failure progressed. This difference between the second and third samples of the controls and the ouabain treated preparations is statistically significant, ($X^2 = 6.19$ $p = 0.01 - 0.02$).

In considering that a decrease in cholinesterase activity accompanies pentobarbital failure in many experiments, one might suppose pentobarbital to be a cholinesterase inhibitor under certain conditions. In our hands, however, pentobarbital has no inhibitory effect in concentrations ranging from 3×10^{-3} M to 1.7×10^{-6}M on true or pseudocholinesterase in dog heart muscle in vitro. On the other hand Genuit and Labenz[22] have demonstrated an inhibition by barbiturates of the ability of the isolated heart to break down acetylcholine.

Rationalization of these opposing facts may require examination of the choline acetylase end of the choline cycle. McLennan and Elliott[23] have demonstrated that barbiturates inhibit choline acetylase. Therefore, a positive inotropic effect should result when a cholinesterase substrate is supplied to the muscle. In our hands, however, benzoylcholine does not produce a positive inotropic effect in the pentobarbital failed heart-lung preparation, nor does the addition of coenzyme A in large quantities. This is not too surprising if, as would appear from Table I, the esterase is in many cases inhibited. Also, it does not necessarily prove that an inhibition of the acetylase may not be operative here.

Mann and associates[19] have indicated that the acetylcholine of the acetylcholine-protein complex cannot be split by cholinesterase. It is possible that such a complex could be inhibitory to the esterase. Thus a block by pentobarbital at the site of the breakdown of this complex would probably prove inhibitory to both Reactions 1 and 3 of Fig. 2 by the accumulation of acetylcholine-protein II. This would be compatible with our finding of a loss or inhibition of cholinesterase in pentobarbital failure as well as with the findings of Elliott and associates that pentobarbital inhibits choline acetylase in vitro[23] and that bound acetylcholine accumulates in the central nervous system during barbiturate anesthesia.[24] Ouabain may act either by liberating the cholinesterase or by facilitating breakdown of acetylcholine-protein II, thus releasing all of the reactions. In this connection Gremels[25] found acetylcholine to be positively ino-

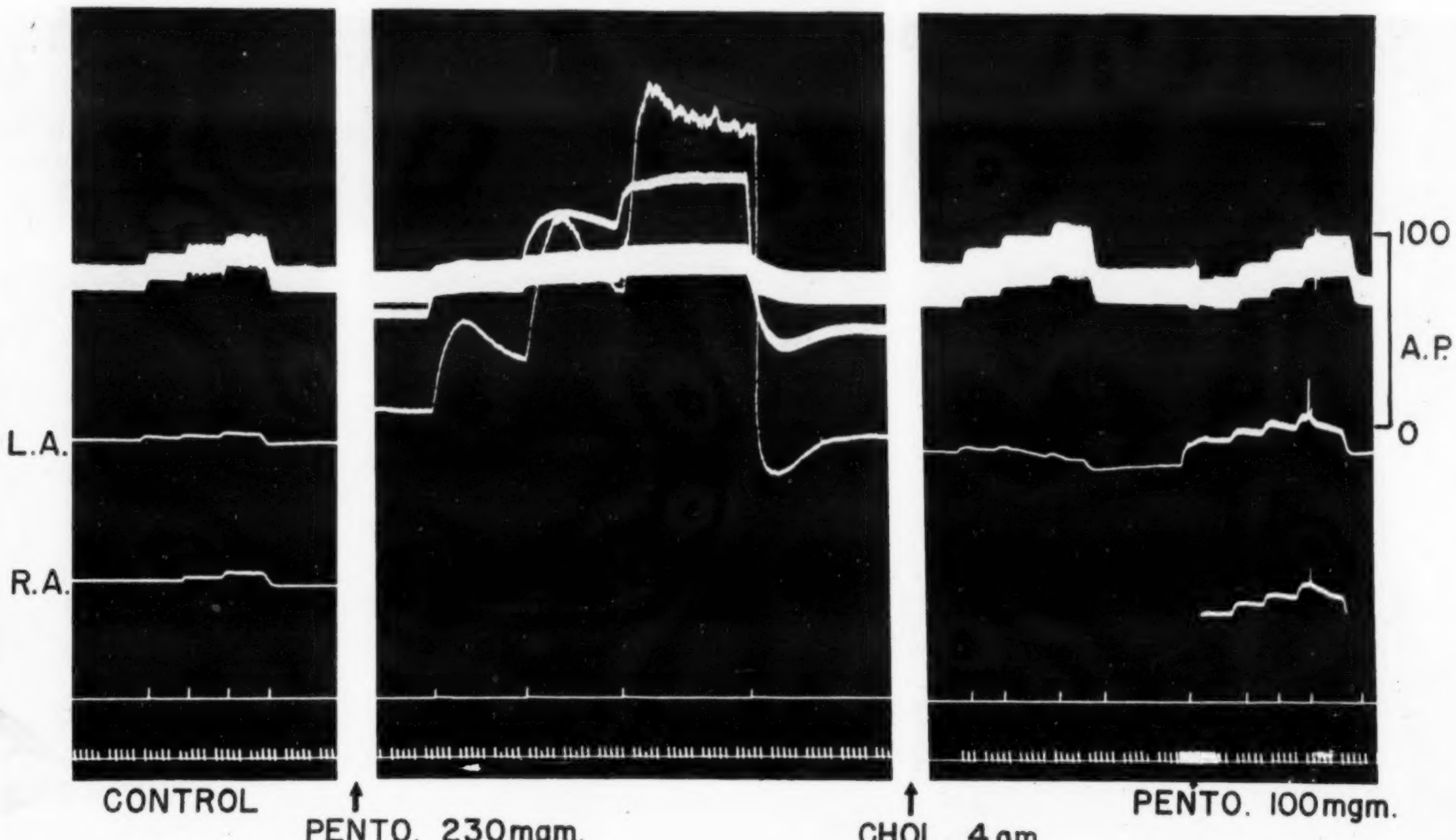

Fig. 4.—Heart-lung Preparation. Dog, male, 18.5 kilograms. Thiopental sodium 20 mg./kg. Atropine sulfate 5.0 mg. Recording from the top: Arterial pressure; left auricular pressure-bromoform manometer; right auricular pressure-water manometer; signal; time in ten-second intervals. Tracing shows responses to elevation of venous reservoir in 5 cm. increments. Arrangement of apparatus did not permit recording of low right auricular pressure in final segment. *Pento.*, Pentobarbital sodium; *Chol.*, choline chloride.

tropic in mammalian hearts and strophanthin to be synergistic with acetylcholine. Bain[26] has suggested that the results of McLennan and Elliott[23] may be explained by an uncoupling of adenosine triphosphate energy supply from the utilization thereof. We have found no change in diphosphopyridine nucleotide and coenzyme A levels before and after pentobarbital failure, which may indicate that the site of barbiturate inhibition is not concerned with the supply or utilization of phosphate bond energy.

If choline acetylase is blocked by pentobarbital and if cholinesterase is inhibited by a substance having not too strong an affinity for the enzyme, the addition of a substrate having a closer affinity for the enzyme prior to the addition of pentobarbital should prevent the negative inotropic effect of pentobarbital. In this connection we have tried benzoylcholine without effect, although it has been found positively inotropic in frog and rabbit hearts by Akcasu and associates.[43] Acetylcholine is positively inotropic, but produces marked cardiac irregularities. Choline itself, however, has marked activity in blocking the negative inotropy of pentobarbital, and has a marked inotropic effect after such failure is produced. Fig. 4 demonstrates this inotropic activity. One might be led to suppose that in this connection choline is serving as substrate for choline acetylase and acetylcholine is being synthesized in such quantities as to bypass an esterase block if it were not for the fact that the enzyme when assayed is supplied with a considerable excess of substrate, and thus no inhibition of esterase should be seen. One must assume that the inhibitory substance (perhaps the acetylcholine-protein complex suggested) has a greater affinity for cholinesterase than does benzoylcholine. Benzoylcholine, although failing to prevent barbiturate decompensation, does block the inotropic effect of choline, although not the inotropic effect of ouabain. It would seem that choline may decrease the affinity of the enzyme for inhibitors, and in turn may itself be blocked off from the enzyme by benzoylcholine.

We have attempted to determine choline acetylase activity in biopsy samples in pentobarbital failure by the method of Feldberg and Mann[27] and have seen a fall in acetylation potential remediable by ouabain in about one-third of the cases. It appears to us that considerable further work is needed with reference to this system; since it seems probable that the in vitro supplying of the biopsy sample with all of the components needed for acetylation may well negate any inhibition obtaining in the heart in situ.

At this point we should like to discuss the eight experiments in Table I in which an apparent stimulation of cholinesterase appeared in failure. We have already pointed out that the operative procedures involved produce a lowering of cholinesterase activity so that one might not expect to see further marked depression of the enzyme after administration of inhibitors. We have also observed that the heart-lung preparations are in poorer condition immediately after the operation than after the lapse of thirty to sixty minutes. It is possible that this phenomenon relates to the presence in the system at the beginning of the experiments of some deleterious substance which is slowly detoxified. The fact that ouabain has an almost universal effect in stimulating dog heart esterase in pentobarbital failure makes it reasonable to believe that the first values are artificially low.

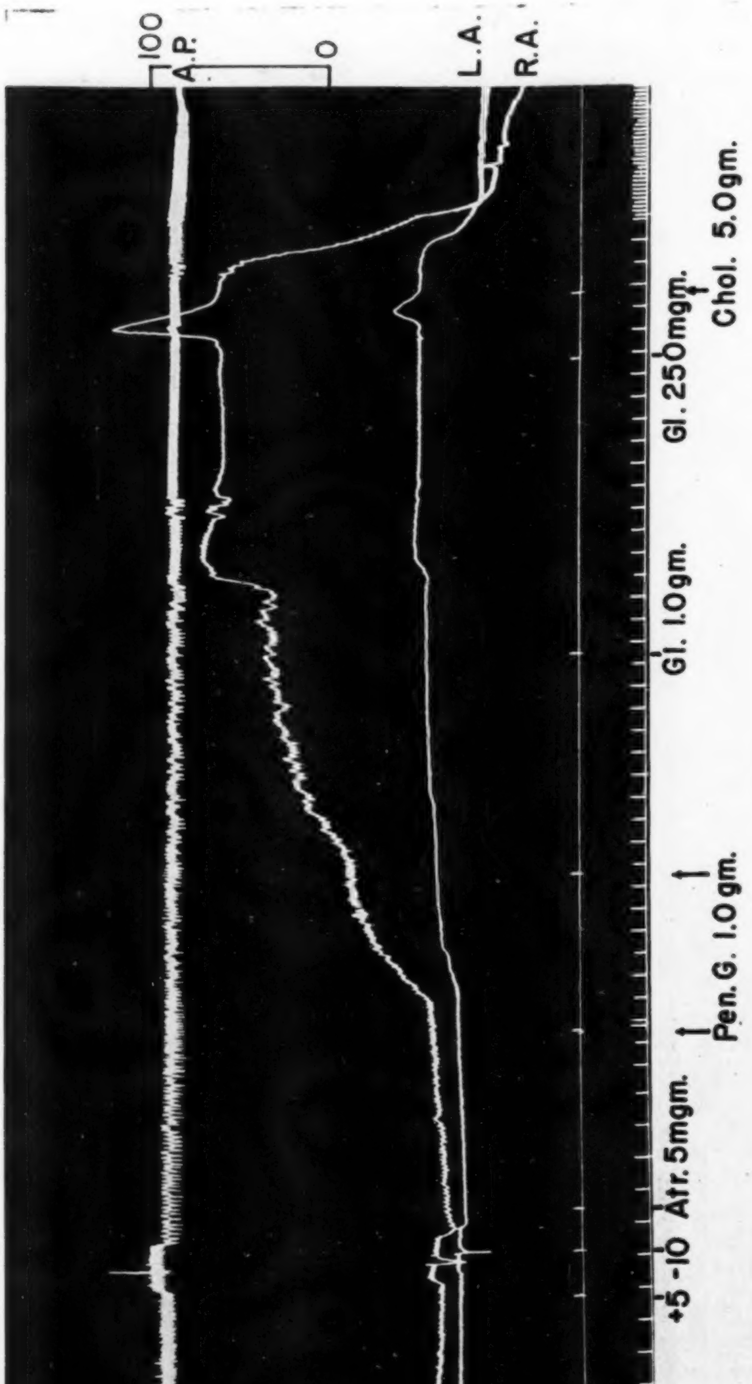

Fig. 5.—Heart-lung preparation. Dog, male, 22.0 kilograms. Thiopental sodium 20 mg./kg. Recording from the top: Arterial pressure; left auricular pressure-water manometer; right auricular pressure-water manometer; signal; time in minutes. +5, +5, −10 response to elevation of reservoir by 5 cm. increments. *Atr.*, Atropine sulfate; *Pen. G.*, penicillin G-potassium; *Gl.*, reduced glutathione; *Chol.*, choline chloride.

B. *The Effect of Penicillin G.*—If one were able to inhibit choline acetylase by means of an inhibitor which acts on Reaction 1 of Fig. 2, thus preventing formation of the acetylcholine-protein complex, cardiac decompensation should occur, with the possibility of bypass of the inhibition by benzoylcholine. Soodak[28] has noted that certain penicillins, among them penicillin G, inhibit acetylation reactions. We have found that marked cardiac decompensation occurs after addition of 1 to 2 Gm. of penicillin G to the reservoir, which can be temporarily reversed in the atropinized preparation by the addition of 100 to 500 mg. of benzoylcholine. This decompensation is rapid and sudden in onset, accompanied by a great deal of cardiac arrhythmia, and poorly remediable by ouabain. In this connection Mosonyi and Porszasz[29] have noted that tachycardia brought on by penicillin therapy in man is not amenable to digitalis therapy, and that penicillin decreases the strength of contraction of the frog heart.

Two penicillin G failure experiments accompanied by heart muscle biopsies have shown no appreciable impairment of cholinesterase activity (Table III). Fig. 5 is a kymogram from a preparation failed with penicillin G and recompensated by choline.

It is unfortunate for our purpose that penicillin G is not an entirely specific acetylase inhibitor. Frommel and associates[30] have shown that cholinesterase is also inhibited. In the presence of very high doses, we too have seen occasional signs of esterase inhibition. Since benzoylcholine is inotropic here, the affinity of penicillin G for the esterase is probably not strong.

Novelli[31] has suggested that penicillin may inhibit choline acetylase by producing a thioclastic split of acetylcoenzyme A, thus preventing transfer of acetyl to choline. This could occur either directly or by the action of penicillamine (dimethyl cysteine) formed on the breakdown of penicillin. Since we have found that penicillamine has no apparent direct effect in the heart-lung preparation it is probably not producing such a thioclastic split. It is interesting however that penicillamine can prevent the negative inotropic effect of penicillin G. Hence, it might be inferred that penicillamine can take the place of cysteine or reduced glutathione in the acetylase mechanism. Glutathione is negatively inotropic in our hands (Fig. 5). Feldberg and Mann[27] have pointed out that reduced glutathione stimulates choline acetylation, but that oxidized glutathione is inhibitory. Although we have administered reduced glutathione, reservoir blood in contact with the agent darkens immediately, indicating that the glutathione is probably oxidized before reaching the cardiac tissues.

Pantoyltaurine, which competes in the utilization of pantothenic acid in the synthesis of coenzyme A, is not significantly inotropic in these experiments.

C. *The Effect of Physostigmine.*—Up to this point we have been dealing with choline acetylase inhibition, and what is possibly an indirect inhibition of cholinesterase. In order to ascertain whether cardiac decompensation can be due to inhibition of cholinesterase, the compound physostigmine, which is commonly considered to be a rather specific cholinesterase inhibitor, was used. In these experiments the preparations were atropinized prior to physostigmine administration.

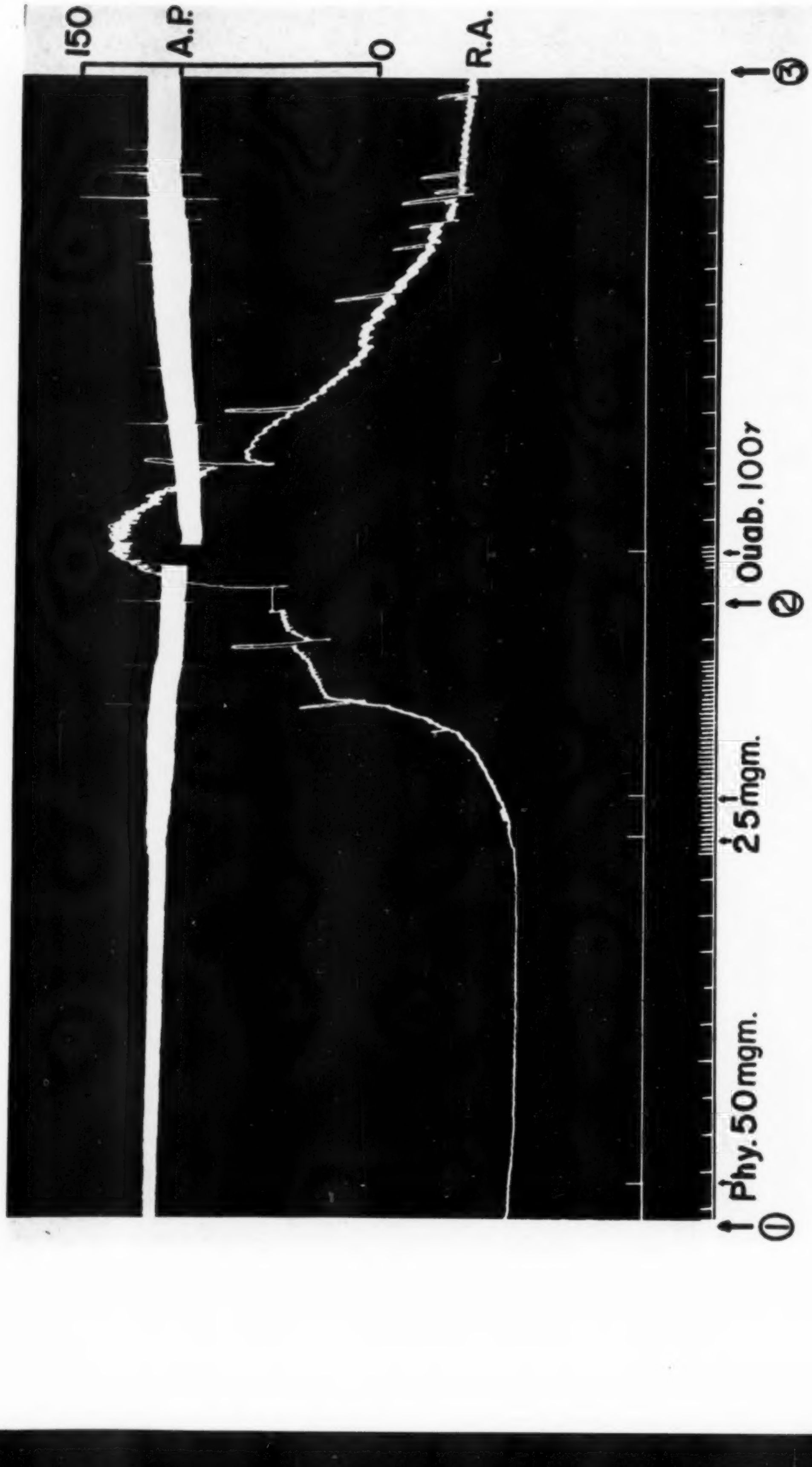

Fig. 6.—Heart-lung preparation. Dog, male; 14.5 kilograms. Thiopental sodium 20 mg./kg. Atropine sulfate 5 mg. Recording from the top: Arterial pressure; right auricular pressure-water manometer; signal; time in minutes. *(1) (2) (3)* Points at which biopsy samples were taken. *Phy.*, Physostigmine base; *Ouab.*, ouabain.

Marked cardiac decompensation was produced by the addition of 60 to 200 mg. of physostigmine (alkaloid) to the reservoir. Additional atropine was not inotropic. The large doses necessary are not too surprising since it has been suggested[32] that the nonspecific enzyme is relatively more difficult to inhibit than is the specific cholinesterase. In addition, the use of large doses of physostigmine enables the production of failure more rapidly than would be possible with smaller amounts. Decompensation by physostigmine can be impeded by previous administration of 1 to 2 Gm. of benzoylcholine, thus blocking access of the inhibitor to the esterase. Fig. 6 shows a kymogram from a preparation failed with physostigmine and treated with ouabain.

If physostigmine is added to the heart-lung reservoir in periodic dosage one might expect to obtain a number of variable results, as pointed out by Krayer and associates,[33] depending chiefly upon the amount of physostigmine added, and the duration of time during which it is allowed to act. Table II shows the possible results of administration of ouabain to such preparations.

TABLE II

SITUATION	RECOVERY OF IN VITRO ESTERASE ACTIVITY AFTER OUABAIN	REDUCTION IN VENOUS PRESSURE AFTER OUABAIN
1.	+	+
2.	−	+
3.	−	−
4.	+	−

Situation 1 would exist when the enzyme is partially inhibited and little excess of physostigmine is circulating. Situation 2 would occur when a considerable excess of uncombined physostigmine is present, which becomes combined during the period elapsing from biopsy to assay of enzyme activity. Situation 3 would obtain if the enzyme is maximally inhibited and a sufficient excess of inhibitor is present to maintain the inhibition. Situation 4 could occur when the second sample is taken soon after a large dose of inhibitor, so that a falsely low value is obtained. This condition would be a variant of Situation 3.

In Table III it may be seen that in fifteen of seventeen experiments cholinesterase becomes inhibited as failure progresses and that occasionally esterase activity increases after ouabain. Most of these experiments showed some drop in venous pressure after ouabain. We believe that we are dealing for the most part with Situation 2 in Table II. Work is in progress to repeat these experiments using the constant rate injection techniques of Krayer. At present we can say only that failure occurs concomitantly with cholinesterase inhibition by physostigmine, that ouabain has a positive inotropic effect to some degree in most cases, and that the esterase inhibition by physostigmine is probably relieved by ouabain if there is not too great an excess of physostigmine in the system.

TABLE III.

(γ ESTER DESTROYED PER MG. DRY WEIGHT PER HOUR)

EXP. NO.	CONTROL SAMPLE	AT FAILURE	AFTER THERAPY	THERAPY	ANESTHESIA	METHOD	ASSAY SUBSTRATE	ATROPINE
PHYSOSTIGMINE FAILURE—CONTROL								
2131-89	52.4	43.1	0	None	PT	Color.	BzCh	+
2131-94	48.4	29.3	16.5	None	PT	Color.	BzCh	+
2131-105	70.9	33.0	29.7	None	PT	Color.	BzCh	+
2131-107	19.1	45.2	31.7	None	PT	Color.	BzCh	+
PHYSOSTIGMINE FAILURE—OUABAIN THERAPY								
2131-20	7.7	2.7	0	Ouabain	PB	Mano.	BzCh	+
2131-23	3.1	0	1.9	Ouabain	PB	Mano.	BzCh	+
2131-26	3.3	0	0	Ouabain	PB	Mano.	BzCh	+
2131-42	62.6	0	0	Ouabain	PT	Color.	BzCh	+
2131-43	41.3	8.1	36.8	Ouabain	PT	Color.	BzCh	+
2131-44	18.6	12.7	23.5	Ouabain	PT	Color.	BzCh	+
2131-112	120.7	79.0	42.4	Ouabain	PT	Color.	BzCh	+
2131-113	81.8	74.9	23.4	Ouabain	PT	Color.	BzCh	+
2131-114	60.3	89.0	20.5	Ouabain	PT	Color.	BzCh	+
PHYSOSTIGMINE FAILURE—CHOLINE THERAPY								
2055-135	12.7	2.5	4.2	Choline	PB	Mano.	AcCh	+
2055-138	11.7	4.9	5.2	Choline	PB	Mano.	AcCh	+
2055-141	13.9	4.1	5.1	Choline	PB	Mano.	AcCh	+
2055-144	9.6	4.1	5.6	Choline	PB	Mano.	AcCh	+
DIISOPROPYL FLUOROPHOSPHATE FAILURE—OUABAIN THERAPY								
2055-32	12.5	7.7	3.9	Ouabain	PB	Mano.	AcCh	—
2055-42	27.2	9.8	3.8	Ouabain	PB	Mano.	AcCh	—
2055-44	22.7	6.6	6.2	Ouabain	PB	Mano.	AcCh	—
PENICILLIN G FAILURE—CHOLINE THERAPY								
2055-147	11.1	12.3	11.8	Choline	PB	Mano.	AcCh	+
2055-150	14.5	13.9	13.5	Choline	PB	Mano.	AcCh	+

For key to abbreviations, see Table I.

D. *The Effect of Diisopropyl Fluorophosphate.*—Diisopropyl fluorophosphate is commonly thought of as an irreversible inhibitor of cholinesterase. This substance was tried in the nonatropinized heart-lung preparation as a means of producing failure. It was found early in the experimentation that a very large dose (25 to 30 mg.) is required for the production of rapid failure (thirty to sixty minutes). A dose of 5 to 10 mg. produces decompensation much more slowly, with gradual rise of venous pressure and onset of pulmonary edema culminating

in severe decompensation two to three hours later. Fig. 7 depicts failure by diisopropyl fluorophosphate, poorly remedied by ouabain.

Some samples of heart muscle removed after diisopropyl fluorophosphate administration but before the onset of failure showed almost complete inhibition of cholinesterase. This finding seemed at first to be in opposition to our theory of failure by cholinesterase inhibition until it was considered, as pointed out by Nachmansohn and associates[34] that diisopropyl fluorophosphate is a fat-soluble substance and requires considerable time for penetration into a watery system such as exists in heart muscle. Free diisopropyl fluorophosphate carried along mechanically in the heart muscle biopsy or dissolved in cardiac fat would be placed in immediate contact with the enzyme on homogenization of the tissue, thus giving an in vitro inhibition which would not necessarily obtain in the heart in vivo. Attempts to wash out the circulating but unbound diisopropyl fluorophosphate, either by replacing the blood containing diisopropyl fluorophosphate with fresh blood in vivo or by washing the homogenates repeatedly showed no evidence of appreciable removal of diisopropyl fluorophosphate. This would suggest that the diisopropyl fluorophosphate may be bound in a fat phase and be poorly diffusible into a water phase on washing. That a certain amount of diisopropyl fluorophosphate is circulating in the blood after decompensation has occurred can be shown by the inhibition of normal heart muscle cholinesterase by the addition of diisopropyl fluorophosphate containing blood from the heart-lung reservoir.

When ouabain was administered to heart-lung preparations treated with diisopropyl fluorophosphate, it was found that a positive inotropic effect was produced when the ouabain was given during moderate failure. When decompensation had become far advanced and the diisopropyl fluorophosphate probably well fixed on the enzyme protein, ouabain had no inotropic effect. Prophylactic administration of ouabain did not prevent ultimate failure by diisopropyl fluorophosphate. Table III demonstrates the fall in cholinesterase activity after diisopropyl fluorophosphate, and the lack of relief by ouabain in three experiments.

The concept of a lag in fixation of diisopropyl fluorophosphate by cholinesterase is supported by the work of Nachmansohn and associates[34] who showed that diisopropyl fluorophosphate inhibition is reversible for a time, depending on the temperature, the duration of exposure, and the concentration of the diisopropyl fluorophosphate. Aldridge[35] after modifying the method of dilution was unable to confirm this, whereas Wilson and associates[36] have been able to show reversibility of the inhibition produced by the analogous substance, tetraethyl pyrophosphate, by a neucleophilic substitution reaction using water, hydroxylamine, or choline.

It should be mentioned that rapid death can be produced in the whole animal by the administration of much smaller doses of diisopropyl fluorophosphate than we have used. This would mean only that diisopropyl fluorophosphate is able to penetrate some vital tissues, such as brain, much more readily than it can approach the esterase of heart muscle.

In the atropinized heart-lung preparation, diisopropyl fluorophosphate produces decompensation similar to that produced by physostigmine, with

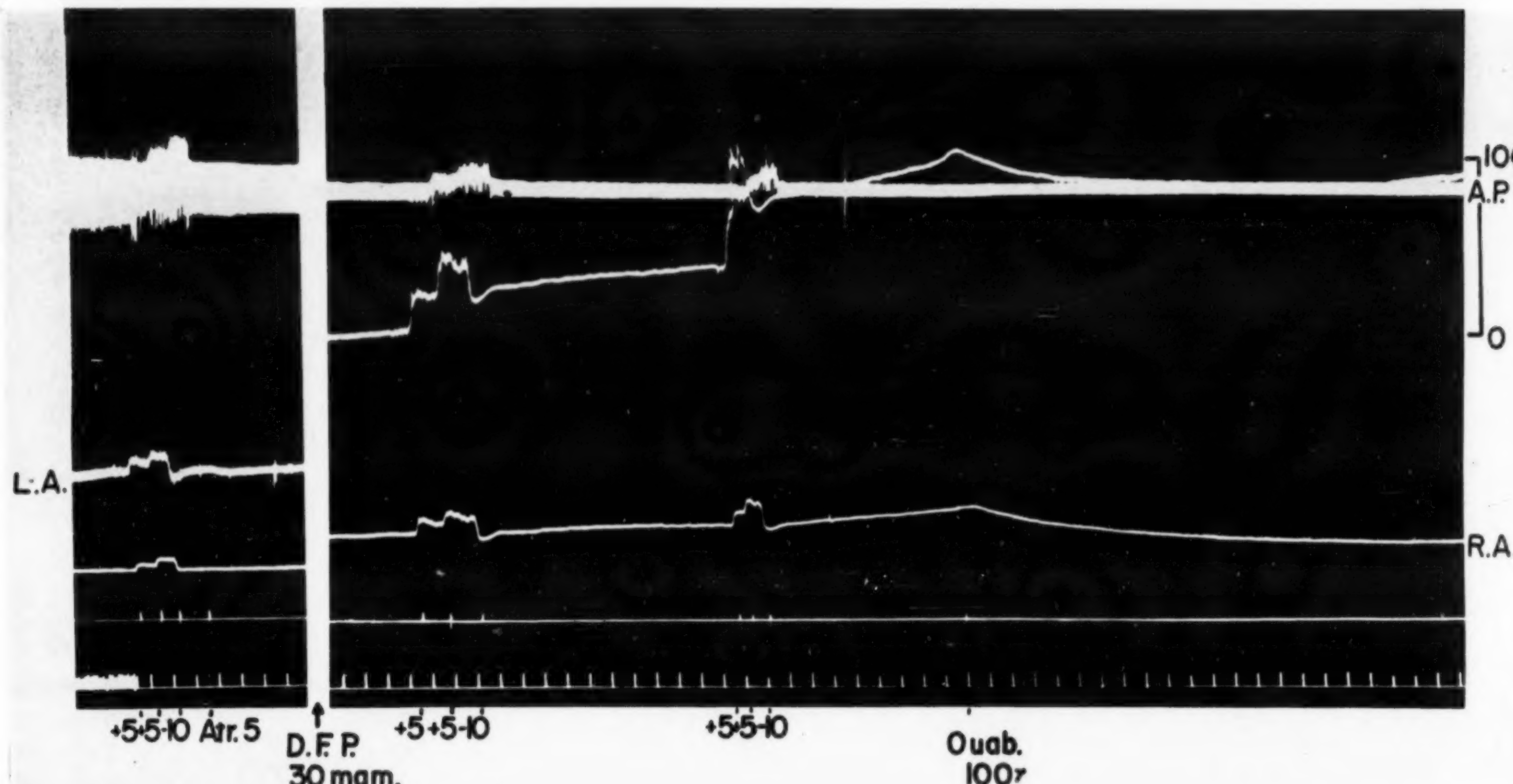

Fig. 7.—Heart-lung preparation. Dog, male, 16.0 kilograms. Thiopental sodium, 20 mg./kg. Recording from the top: Arterial pressure, left auricular pressure-water manometer; right auricular pressure-water manometer; signal; time in minutes. *Atr. 5*, Atropine sulfate 5 mg.; *D.F.P.*, diisopropyl fluorophosphate; *Ouab.*, ouabain.

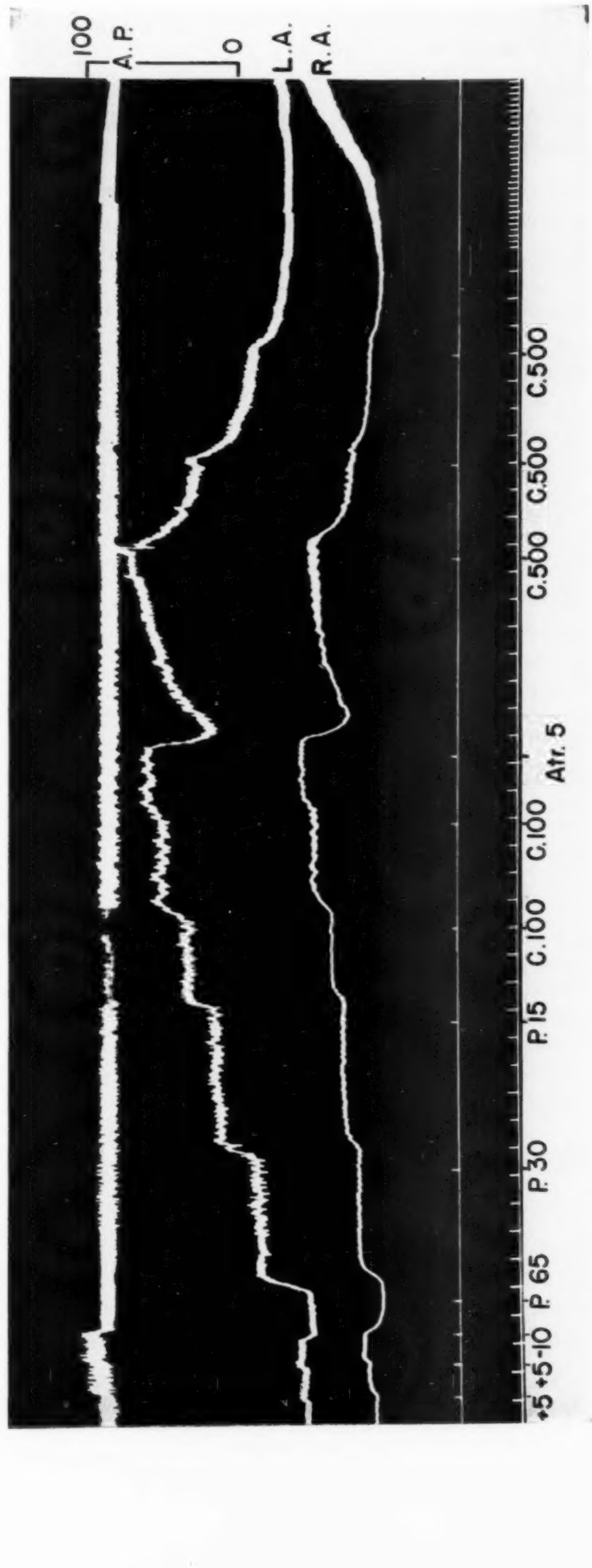

Fig. 8.—Heart-lung preparation. Dog, male, 16.0 kilograms. Thiopental sodium 20 mg./kg. Recording from the top: Arterial pressure; left auricular pressure-bromoform manometer; right auricular pressure-water manometer; signal; time in minutes. All doses in milligrams. *P.*, pentobarbital sodium. *C.*, choline chloride; *Atr.*, atropine sulfate.

minimal pulmonary edema and with left ventricular failure predominant. This type of failure responds poorly to ouabain.

Thiamin triphosphate and phosphorylcholine were found to be negatively inotropic, which is not surprising in view of their relationship to the phosphorylated cholinesterase inhibitors.

E. *The Effect of Choline.*—In the nonatropinized heart-lung preparation with failure by these methods, choline was negatively inotropic. However in the atropinized preparation, choline in this dose demonstrated strong and rapid positive inotropic action after decompensation produced by pentobarbital,* physostigmine, diisopropyl fluorophosphate, and penicillin G. An example of this dual action of choline is shown in Fig. 8. The administration of large doses (5 Gm.) of choline also deters recurrence of myocardial decompensation produced by administration of physostigmine or pentobarbital in the amounts of 100 to 200 mg., although pulmonary edema usually ensues after the physostigmine. The effect of choline can be blocked by previous administration of benzoylcholine. The positive inotropic effect of choline is accompanied by an increase in cholinesterase activity.

There are several possible explanations for the positive inotropy and increase in cholinesterase activity produced by choline.

1. Choline may serve as substrate for synthesis of acetylcholine, thus producing either large enough amounts of acetylcholine to displace inhibitors, or acetylcholine in favorable proximity to the enzyme. This thought would force the assumption that injected acetylcholine or acetylcholine added in the enzyme assay would not reach the esterase, since the assay for esterase activity is carried out in the presence of a large excess of substrate.

2. Wilson[36d] has postulated that choline, hydroxylamine, or water can relieve alkylphosphate inhibition of cholinesterase by a nucleophilic substitution reaction, the net effect of which would be the phosphorylation of the choline. This explanation may apply to relief of diisopropyl fluorophosphate failure by choline, but probably not to relief of physostigmine or pentobarbital failure.

3. On the basis of the work by Wilson and associates[36c] it is conceivable that addition of choline chloride (which we have employed) in large amounts to the heart-lung reservoir may lower the pH enough to change the affinity of the enzyme for the inhibitor so as to prevent combination. Experiments in which blood pH was measured before and after choline chloride showed no significant deviation from pH 8. We are unable to say whether or not blood pH is an accurate reflection of tissue pH in this case.

4. As Frommel and associates[21] have postulated for betaine, the combination of choline with "receptor substances" may have an ionic character, and choline may be substituting for Na, Ca, or K in situations when one of these ions is lost due to failure of the cholinesterase-acetylcholine system.

5. A less probable explanation may lie in the stimulation by choline of sympathetic ganglion cells said to exist in the heart.[37]

The ionic explanation of Frommel appears to us to be closest to the proper one. This would place choline in the role of a substance able to bypass a failing cholinesterase ion transfer system with the added advantage of serving as a substrate for acetylcholine synthesis. This concept may explain the positive

*It has come to our attention since submission of this manuscript that this action of choline was pointed out by Krayer, Farah, and Uhle, J. Pharmacol & Exper. Therap. 88:277, 1946.

inotropic effect of tetraethylammonium noted by Acheson and Moe,[38] although the latter substance could not serve as substrate for acetylcholine synthesis.

It should be mentioned that Abdon and Borglin[39] have noted bradycardia, sudden death, and a sudden drop in acetylcholine precursor in choline deficient rats. These authors believe the reaction acetylcholine precursor → acetylcholine to be necessary to heart metabolism.

III. *Site of Action of Compounds Influencing the Choline Cycle and the Possible Etiology of Decompensation.*—On the basis of these findings one is led to postulate that interference in the choline cycle can result in cardiac decompensation in the dog heart-lung preparation, whether this interference be at the site of formation of acetylcholine, or at the site of its breakdown. Pentobarbital would appear to act by inhibition in the choline acetylase system, possibly by interfering with breakdown of an acetylcholine-protein complex, thus depriving the heart muscle of a substrate for the maintenance of cell membrane integrity. Penicillin G may achieve the same result by interference with actual acetylation of choline. Physostigmine and diisopropyl fluorophosphate prevent metabolism of acetylcholine by esterase inhibition. Choline appears to relieve cholinesterase inhibition. Ouabain may be presumed to act by relieving esterase inhibition and not by promoting breakdown of bound acetylcholine since it is somewhat inotropic in physostigmine and diisopropyl fluorophosphate failures, where inhibition by bound acetylcholine is probably not important. These concepts of the mechanism of ouabain action are evidenced by the poor inotropic effect of ouabain seen in penicillin, advanced physostigmine, and advanced diisopropyl fluorophosphate failure, as well as by the absence of ouabain positive inotropy in the normal heart. The possible sites of action of all of these compounds can be illustrated as follows:

Choline as substrate? ↓ Penicillin G, acetylcholine-protein II ↓

1. Acetyl ∼ Co A – protein I + choline-protein II ——→ Co A + protein I + Acetylcholine-protein II

Pentobarbital ↓

2. Acetylcholine-protein II ——→ acetylcholine + protein II

3. Acetylcholine ——→ choline + acetyl
esterase
↑ ←—Ouabain, choline
Physostigmine, diisopropyl fluorophosphate, acetylcholine-protein II, penicillin G

The points in support of the hypothesis that the choline cycle plays an important role in cardiac decompensation may be summarized in the following manner:

1. Inhibitors of cholinesterase produce cardiac decompensation which is accompanied by a measurable decrease in the nonspecific cholinesterase activity of the heart muscle.

2. Ouabain produces, to a variable degree, both positive inotropy and relief of esterase inhibition in decompensation produced by cholinesterase inhibitors. This variability probably depends on the degree of fixation of inhibitor by the enzyme protein.

3. Penicillin, a choline acetylase inhibitor, produces cardiac decompensation not remediable by ouabain.

4. Pentobarbital produces cardiac decompensation with frequent inhibition of nonspecific cholinesterase. Since pentobarbital is an in vitro inhibitor of choline acetylase and not of pseudocholinesterase, the esterase inhibition seen here is probably indirect. Pentobarbital decompensation is remediable by ouabain, and ouabain administration is followed by a maintenance of or an increase in cholinesterase activity.

5. Benzoylcholine, an esterase substrate, is positively inotropic in failure produced by acetylase inhibition, and in addition impedes decompensation by cholinesterase inhibitors.

6. Choline, which may be considered to activate cholinesterase ionically or to bypass the poorly functioning esterase system, is positively inotropic in atropinized preparations failed by either cholinesterase or choline acetylase inhibitors.

These data also allow hypothesis as to the cardiac actions of Ca^{++}, K^{+}, and that controversial substance, α-tocopherol.

Ca^{++} is well known for its positive inotropic effect and has been shown to activate both true and pseudocholinesterases (Mendel and associates,[40] Nachmansohn.[41]) K^{+} has an activating effect on true cholinesterase (Mendel and Rudney[42]) but inhibits the nonspecific enzyme (Mendel and associates[40]) which is the enzyme under consideration in these experiments. This may account for its marked negative inotropism. Tocopherol-free diets have been shown by Bloch[43] to lower cholinesterase activity in brain, serum, and liver, and in addition, Torda and Wolff[44] have described a marked stimulation of choline acetylase by α-tocopherol. It is conceivable that some individuals may be sufficiently vitamin E deficient as to respond to the administration of the substance by improved cardiac function.

It is apropos to mention the well-known and extensive work of Burn and associates[45] who have investigated acetylcholine as a local hormone. Burn has shown that acetylcholine can restart the nonbeating rabbit heart and that synthesis of acetylcholine is necessary for auricular contraction. The inhibitory effect of added acetylcholine on acetylcholine synthesis and on auricular contraction in the unfailed heart which he describes can possibly be explained as an inhibition of cholinesterase by excess substrate (considering the esterase to be capable of either synthesis or hydrolysis[34]). The stimulatory effect of added acetylcholine on the heart muscle and on the synthesis of acetylcholine in the failed heart can be related not only to the conduction system and pacemaker as postulated by Burn, but also to the restoration of cell membrane integrity by the supplying of cholinesterase substrate in the presence of a deficiency thereof.

SUMMARY

1. The cholinesterase occurring in dog heart muscle is predominantly of the nonspecific type.

2. Pentobarbital failure is often accompanied by a decreased cholinesterase activity in the heart muscle.

3. Ouabain administration to the heart decompensated by pentobarbital results in a maintenance of or an increase in cholinesterase activity concomitantly with its positive inotropic effect.

4. Decompensation can be produced by large doses of penicillin G, physostigmine, or diisopropyl fluorophosphate, agents known to be inhibitory in the choline cycle. Failure by penicillin G is poorly remediable by ouabain. Ouabain is effective to a variable degree in physostigmine and diisopropyl fluorophosphate failure.

5. Choline in large doses is positively inotropic in the atropinized dog heart-lung preparation failed by any of these compounds. Its administration hinders subsequent failure by physostigmine or pentobarbital, and results in a partial relief of physostigmine inhibition of cholinesterase.

6. Benzoylcholine has positive inotropic activity in failure produced by penicillin G and impedes decompensation by physostigmine. Benzoylcholine inhibits the positive inotropic effect of choline.

7. Ouabain may function to relieve esterase inhibition or (less likely) to release acetylcholine from its protein complex.

8. The hypothesis is offered that these types of decompensation are the result of interference with the choline cycle as it pertains to cell membrane integrity, and that other types of decompensation may have a similar etiology.

REFERENCES

1. Wollenberger, A.: The Energy Metabolism of the Failing Heart and the Metabolic Action of the Cardiac Glycosides, Pharmacol. Rev. **1**:311, 1949.
2. Harrison, T. R., Pilcher, C., and Erving, G.: The Potassium Content of Skeletal and Cardiac Muscle, J. Clin. Investigation **8**:325, 1930.
3. Calhoun, J. A., and Harrison, T. R.: The Effect of Digitalis on the Potassium Content of the Cardiac Muscle of Dogs, J. Clin. Investigation **10**:139, 1931.
4. Cattell, McK., and Goodell, H.: On the Mechanism of the Action of Digitalis Glucosides on Muscle, Science **86**:106, 1937.
5. Wood, E. H., and Moe, G. K.: Studies of the Effect of the Digitalis Glucosides on Potassium Loss From the Heart of the Heart-Lung Preparation, Am. J. Physiol. **123**:219, 1938.
6. Mangun, G. H., and Myers, V. C.: Creatine, Potassium, and Phosphorus Content of Cardiac and Voluntary Muscle, Proc. Soc. Exper. Biol. & Med. **35**:455, 1936.
7. Boyer, P. K., and Poindexter, C. A.: The Influence of Digitalis on the Electrolyte and Water Balance of Heart Muscle, AM. HEART J. **20**:586, 1940.
8. Calhoun, J. A., Cullen, G. E., and Harrison, T. R.: The Effect of Overwork on the Potassium Content of Skeletal Muscle, J. Clin. Investigation **9**:405, 1930.
9. Fenn, W. O., Cobb, D. M., Manery, J. F., and Bloor, W. R.: Electrolyte Changes in Cat Muscle During Stimulation, Am. J. Physiol. **121**:595, 1938.
10. Tipton, S. R.: The Effect of Cortin on the Electrolyte Changes in Cat Muscle During Stimulation and Recovery, Am. J. Physiol. **124**:322, 1938.
11. Zwemer, R. L., and Truszkowski, R.: The Importance of Corticoadrenal Regulation of Potassium Metabolism, Endocrinology **21**:40, 1937.
12. Zwemer, R. L., and Loewenstein, B. E.: Cortin-Like Effect of Steroid Glycosides on Potassium, Science **91**:75, 1940.
13. (a) Greig, M. E., and Holland, W. C.: The Relationships Between Cholinesterase Activity and Permeability of Dog Erythrocytes, Arch. Biochem. **23**:370, 1949.

(b) Greig, M. E., and Holland, W. C.: The Effect of d and l-isomers of Isoamidone on the Permeability of Dog Erythrocytes, Proc. Soc. Exper. Biol. & Med. **71**:189, 1949.
(c) Greig, M. E., and Holland, W. C.: Increased Permeability of the Hemoencephalic Barrier Produced by Physostigmine and Acetylcholine, Science **110**:230, 1949.
(d) Greig, M. E., Holland, W. C., and Lindvig, P. E.: The Anesthetization of the Rabbit's Cornea by Nonsurface Anesthetics, Brit. J. Pharmacol. and Chemotherapy **5**:461, 1950.
(e) Greig, M. E., and Mayberry, T. C.: The Relationship Between Cholinesterase Activity and Brain Permeability, J. Pharmacol. & Exper. Therap. **102**:1, 1951.
(f) Greig, M. E., and Holland, W. C.: Effect of Certain Choline and Noncholine Esters on Permeability of Dog Erythrocytes, Am. J. Physiol. **164**:423, 1951.

14. Augustinsson, K.-B.: Cholinesterases, Acta Physiol. Scandinav. **15**:Suppl., 1948.
15. DuBois, K. P., and Mangun, G. H.: The Effect of Hexaethyl Tetraphosphate on Choline Esterase in Vitro and in Vivo, Proc. Soc. Exper. & Biol. Med. **64**:137, 1947.
16. Hestrin, S: Reaction of Acetylcholine and Other Carboxylic Acid Derivatives With Hydroxylamine and Its Analytical Applications, J. Biol. Chem. **180**:249, 1949.
17. Stadtman, E. R., Novelli, G. D., and Lipmann, F.: Coënzyme A Function in and Acetyl Transfer by the Phosphotransacetylase System, J. Biol. Chem. **191**:365, 1951.
18. Mann, P. J. G., Tenenbaum, M., Quastel, J. H.: Acetylcholine Metabolism in the Central Nervous System, Biochem. J. **33**:822, 1939.
19. Mann, P. J. G., Tenenbaum, M., and Quastel, J. H.: On the Mechanism of Acetylcholine Formation in Brain in Vitro, Biochem. J. **32**:237, 1938.
20. Bergmann, F., and Shimoni, A.: The Changes in the Nerve Membrane and the Role of Choline Esterase in the Conductive Process, Biochim. et biophys. acta **8**:352, 1952.
21. Frommel, E., Hirschberg, A. D., and Picquet, J.: Effects des ions inorganiques sur l'activité de la Cholinestérase sérique, Helvet. Physiol. Pharmacol. Acta **2**:169, 1944.
22. Genuit, H., and Labenz, K.: Über die Wirksamkeit der Cholinesterase im intakten Herzmuskel des Warmbluters und ihre Beeinfluszbarkeit durch verschiedene Pharmaka, besonders die Narkotica, Arch. f. exper. Path. u. Pharmakol. **198**:369, 1941.
23. McLennan, H., and Elliott, K. A. C.: Effects of Convulsant and Narcotic Drugs on Acetylcholine Synthesis, J. Pharmacol. & Exper. Therap. **103**:35, 1951.
24. Elliott, K. A. C., Swank, R. I., and Henderson, Nora: Effects of Anesthetics and Convulsants on Acetylcholine Content of Brain, Am. J. Physiol. **162**:469, 1950.
25. Gremels, Hans: Ueber den Einfluss von Digitalisglykosiden auf die energetischen Vorgaenge am Sauegetierherzen, Arch. f. exper. Path. u. Pharmakol. **186**:625, 1937.
26. Bain, J. A.: Enzymatic Aspects of Barbiturate Action, Federation Proc. **11**:653, 1952.
27. Feldberg, W., and Mann, T.: Formation of Acetylcholine in Cell-free Extracts From Brain, J. Physiol. **104**:8, 1945.
28. Soodak, M.: Abstract, Div. Biol. Chem., Amer. Chem. Soc., 119th Meeting, Boston, 18C, April, 1951.
29. Mosonyi, L., and Porzasz, J.: Digitalis Sensitivity of Persons Treated With Penicillin, Orvosi Hetil. **89**:149, 1948. Chemical Abstracts **43**:8547h.
30. Frommel, E., Goldféder, A., and Piquet, J.: Some Secondary Effects of Penicillin Upon Experimental Animals: Influence on Cholinesterase and Ascorbic Acid, Acta pharmacol. et toxicol. **2**:207, 1946.
31. Novelli, G. D.: Personal communication.
32. Gilman, A., Carlson, R. I., and Goodman, L.: Specific and Non-Specific Cholinesterase in Rat Tissues, J. Pharmacol. & Exper. Therap. **66**:14, 1939.
33. Krayer, O., Goldstein, A., and Plachte, F. L.: Quantitative Relation Between Dosage of Physostigmine and Inhibition of Cholinesterase Activity in the Blood Serum of Dogs, J. Pharmacol. & Exper. Therap. **80**:8, 1944.
34. Nachmansohn, D., Rothenberg, M. A., and Feld, E. A.: The in Vitro Reversibility of Cholinesterase Inhibition by Diisopropyl Fluorophosphate, Arch. Biochem. **14**:197, 1947.
35. Aldridge, W. N.: Some Properties of Specific Cholinesterase With Particular Reference to the Mechanism of Inhibition of Diethyl p-Nitrophenyl Thiophosphate (E605) and Analogues, Biochem. J. **46**:451, 1950.
36. (a) Wilson, I. B., and Bergmann, F.: Studies on Cholinesterase. VII. The Active Surface of Acetylcholine Esterase Derived From Effects of pH on Inhibitors, J. Biol. Chem. **185**:479, 1950.
(b) Wilson, I. B., and Bergmann, F.: Acetylcholinesterase. VIII. Dissociation Constants of the Active Groups, J. Biol. Chem. **186**:683, 1950.
(c) Wilson, I. B., Bergmann, F., and Nachmansohn, D.: Acetylcholinesterase X. Mechanism of the Catalysis of Acylation Reaction, J. Biol. Chem. **186**:781, 1950.

(d) Wilson, I. B.: Acetylcholinesterase. XI. Reversibility of Tetraethyl Pyrophosphate Inhibition, J. Biol. Chem. **190**:111, 1951.

(e) Wilson, I. B., Levine, S., and Freiberger, I.: Effects of Electrical Charge Upon the Activity of Liver Esterase, J. Biol. Chem. **194**:613, 1952.

37. Hoffmann, E. J., Middleton, S., and Talesnik, J.: The Stimulating Effect of Acetylcholine on the Mammalian Heart and the Liberation of an Epinephrine-like Substance by the Isolated Heart, Am. J. Physiol. **144**:189, 1945.

38. Acheson, G. H., and Moe, G. K.: Some Effects of Tetraethyl Ammonium on the Mammalian Heart, J. Pharmacol. & Exper. Therap. **84**:189, 1945.

39. Abdon, N. O., and Borglin, N. E.: On the Mechanism of Choline Deficiency, Acta Pharmacol. et toxicol. **3**:73, 1947.

40. Mendel, B., Mundell, D. B., and Strelitz, F.: Cholinesterase and Electrolytes, Nature, London **144**:479, 1939.

41. Nachmansohn, D.: Action of Ions on Cholinesterase, Nature, London, **145**:513, 1940.

42. Mendel, G., and Rudney, H.: Some Effects of Salts on True Cholinesterase, Science **102**:616, 1945.

43. Bloch, H.: Influence of Vitamin E Deficiency on Activity of Cholinesterase, Helv. Chim. acta **25**:793, 1942.

44. Torda, C., and Wolff, H. G.: Effect of Vitamins on Acetylcholine Synthesis. The Apparently Specific Action of Vitamin E, Proc. Soc. Exper. Biol. & Med. **58**:163, 1945.

45. Burn, J. H.: Relation of Motor and Inhibitor Effects of Local Hormones, Physiol. Rev. **30**:177, 1950.

46. Akcasu, A., Sinha, Y. K., and West, G. B.: The Pharmacology of Benzoylcholine, Brit. J. Pharmacol. **7**:331, 1952.

Clinical Reports

EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE

J. F. Goodwin, M.D., M.R.C.P., Allan Wynn, M.D., M.R.C.P., and
R. E. Steiner, M.B., D.M.R.

London, England

THE OBJECT of this paper is to present a case of Ebstein's syndrome in which the diagnosis was made in life and confirmed at autopsy. Special reference will be made to certain diagnostic criteria, and these will be compared and contrasted with those found in a probable second case, still living. A case of pulmonary stenosis with normal aortic root and right-to-left interatrial shunt will also be discussed, in view of certain angiocardiographic features resembling Ebstein's syndrome.

Case 1.—The patient was a boy of 14, who had always been dyspneic on exertion. His dyspnea had greatly increased since the age of 12, until his effort tolerance was reduced to only one hundred yards. Cyanosis and squatting were also noted from the same age.

Physical examination revealed an asthenic youth, with a high arched palate. He had cyanosis, but no clubbing; bulging sternum; small pulse, and blood pressure of 120/80 mm. Hg. His cardiac pulsation was diffuse, gentle and indefinite in type. There was a systolic murmur at all areas, a diastolic triple rhythm to the left of the sternum, a faint low-pitched mid-diastolic murmur at the apex, and jugular venous pressure showed large "A" and "V" waves. The liver was not enlarged nor pulsating.

Investigation disclosed the following:

1. *Blood*: Hemoglobin 18.2 Gm. per cent, and arterial oxygen saturation 81 per cent.

2. *Fluroscopy* (Fig. 1) showed a gross right auricular enlargement and questionable right ventricular enlargement. Main pulmonary arteries were difficult to visualize, and the lungs were underfilled.

3. *Electrocardiogram* (Fig. 2) showed a complete right bundle branch block.

4. *Phonocardiogram* (Fig. 3). *Second left intercostal space*: Three heart sounds were present here. The first element of this triple rhythm coincided with the A wave of the jugular phlebogram; no true first heart sound was evident; a short late systolic murmur merged with the vibrations of the second sound, which was split, and an added sound was present in early diastole. *Anterior axillary line*: In this area four sounds were present, these being a sound in presystole, first and second heart sounds, a sound in early diastole, and there was also a late systolic murmur.

5. *Angiocardiogram* (Fig. 4, *A* and *B*). The contrast medium filled the whole of the heart shadow within a few seconds after the start of the injection in the posteroanterior view, forming a rounded opacity suggesting a very large right auricle. There was marked delay in emptying of this chamber, and at seventeen seconds no pulmonary artery filling could be detected.

From the Departments of Medicine and Radiology, Postgraduate Medical School of London, England.

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6. *Circulation times.* These were as follows: arm-to-tongue (saccharin), twenty-two seconds; arm-to-lung (paraldehyde), twenty-one seconds.

Diagnosis.—The boy had Ebstein's malformation of the tricuspid valve to a severe degree, and interatrial communication with right-to-left shunt.

Progress.—It was felt that, since the prognosis was poor, a subclavian pulmonary artery anastomosis was justifiable, and the operation was performed by Mr. W. P. Cleland. During the procedure the patient became more cyanosed and the blood pressure fell sharply. In spite of this the operation was concluded satisfactorily, and his general condition was good on return to the ward. In early hours of the next morning, however, the patient suddenly became extremely cyanosed and dyspneic, the blood pressure fell suddenly, and he died in a few minutes.

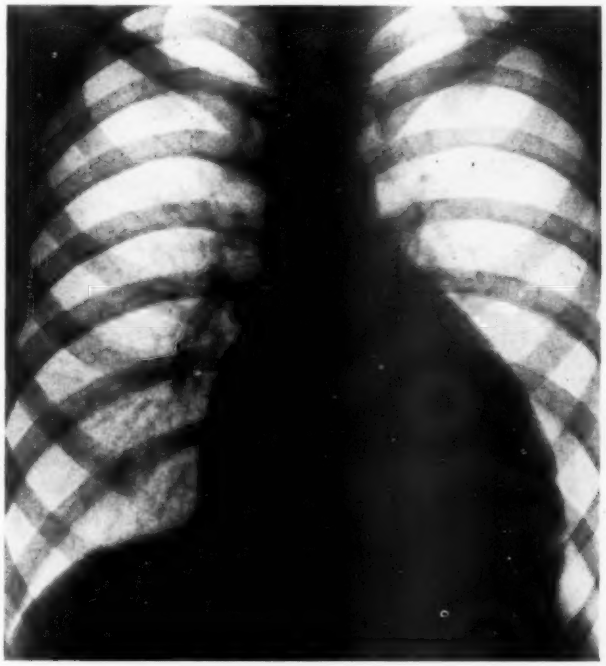


Fig. 1 (Case 1).—Plain roentgenogram of chest which indicates a large globular heart, large right auricle, and (?) right ventricle; Pulmonary arteries are not enlarged, and lungs are underfilled.

*Autopsy** (Fig. 5).—The heart was enlarged, measuring 13 cm. vertically and 13 cm. horizontally. There was a very early pericarditis. The right atrium was a little dilated (45 mm. maximum vertical diameter) and hypertrophied to a maximum thickness of 6 cm. The foramen ovale was patent, with a diameter of about 8 mm. The right ventricle[2] was greatly dilated and 4 to 5 mm. thick. The tricuspid ring was dilated. On its posterior and septal wall there was no valve cusp but on its anterior wall there was a large membranous curtain about 70×60 mm.[1] This was attached above to the anterior part of the tricuspid ring, laterally along a line running down the outer part of the posterior wall of the ventricle, and medially to the septum about 20 mm. behind the junction of the latter with the anterior wall of the ventricle. Near the apex of the ventricle there was an aperture between the valve curtain and the posterior ventricular wall[3] about 10 mm. in diameter. There was a second, larger aperture, about 3×2 cm., between the valve curtain and the septum in the conus region 20 mm. below the top of the pulmonary valve cusps.[5] These two apertures formed the only communication between the atrium and ventricle. The pulmonary valve and artery[4] were normal but a Blalock anastomosis had been made between

*Autopsy performed by Dr. C. V. Harrison.

the left pulmonary and the left subclavian arteries. The left atrium and mitral valve were normal. The left ventricle was small, being 10 to 12 mm. thick. Histologic examination of both atria and both ventricles confirmed the pericarditis and the hypertrophy of the right auricle, but did not show any other abnormality.

CASE 2.—The patient was a 13-year-old boy, who had slight cyanosis since birth, slight to moderate dyspnea on exertion, no squatting, and he attended normal school.

Upon *examination* he proved to be a slightly undersized, active, intelligent boy. He had slight cyanosis and no clubbing. His heart was diffusely enlarged to the right and left of the sternum. The apex beat was left ventricular in type, with no right ventricular heave. There was a moderately harsh systolic murmur and a low-pitched mid-diastolic murmur in the left parasternal region. There were added sounds in early diastole and presystole. There was a single pulmonary second sound which was not accentuated. The jugular venous pressure was normal and the blood pressure was 102/76 mm. Hg.

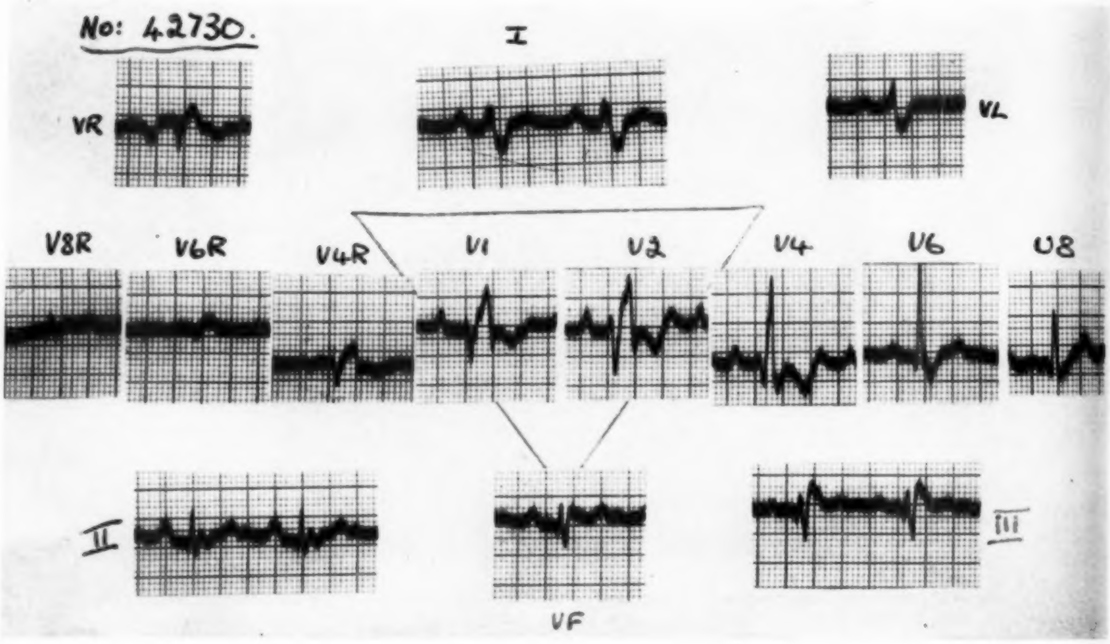


Fig. 2 (Case 1).—Electrocardiogram indicating complete right bundle branch block and auricular hypertrophy (P pulmonale).

Investigation disclosed the following:

1. *Blood.* Hemoglobin was 18 Gm. per cent, and arterial oxygen saturation 88 per cent.

2. *Fluroscopy* (Fig. 6) showed that the heart was globular. The right auricle and possibly the right ventricle were enlarged. The pulsation was not marked, the lungs were underfilled, and the pulmonary arteries were small.

3. *Electrocardiogram* (Fig. 7). The appearances were compatible with normality at that age, but there was a secondary R wave in leads V_{4R} and V_1, suggesting incomplete right bundle branch block.

4. *Circulation time.* From the arm to the lung, seven seconds (ether). From the arm to the tongue, nineteen seconds (saccharin.).

5. *Angiocardiogram* (Fig. 8, *A* and *B*). A large right auricle could be seen and opacification of the left auricle from the right auricle was evident. There was delay in emptying of the right auricle, and the pulmonary arteries were not well opacified, the lungs being underfilled with contrast medium. The tricuspid notch was displaced to the left and the aorta opacified from the left ventricle. The right ventricle could not be seen clearly in either posteroanterior or lateral views, possibly owing to early filling of the left ventricle from the left auricle.

6. *Cardiac catheterization.* The catheter curled repeatedly in a large right auricle. The right ventricle and the left auricle were not entered. The right auricular mean pressure was 2.5 cm. saline above the sternal angle. There was no evidence of left-to-right interatrial shunt.

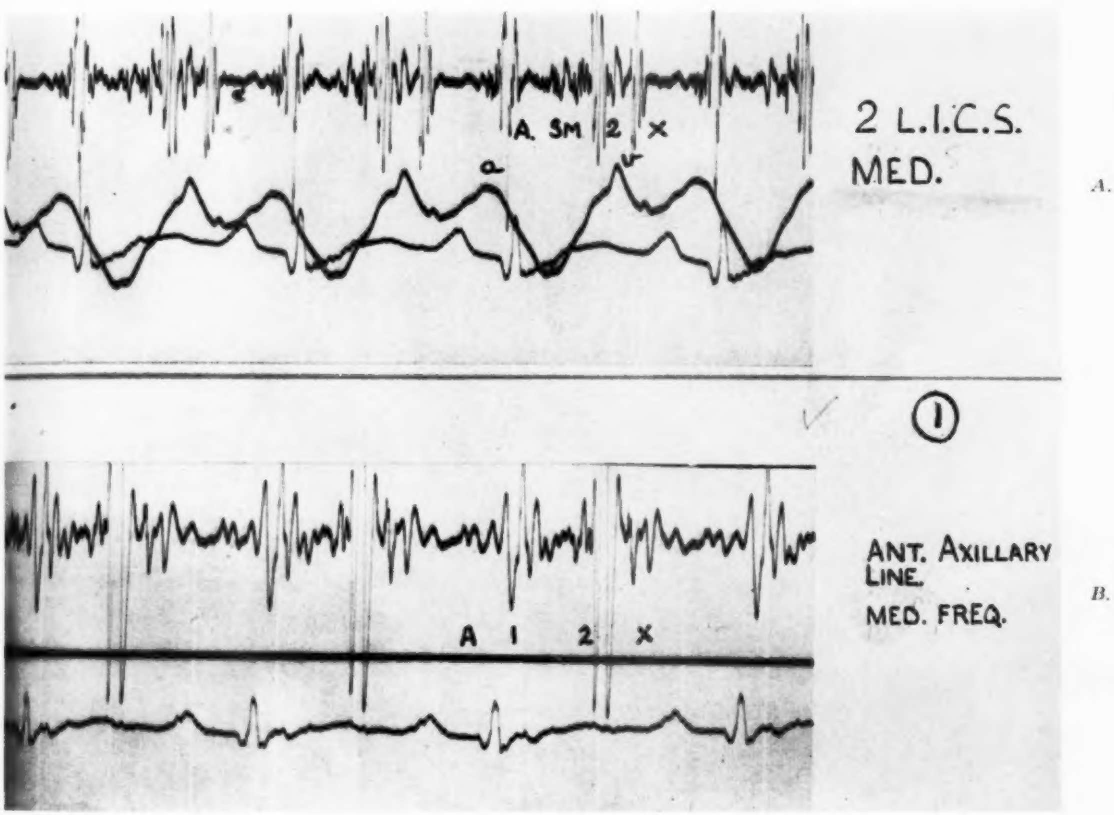


Fig. 3 (Case 1.)—Phonocardiogram, jugular phlebogram, and Lead II of electrocardiogram. *A*, Record taken at left intercostal space; *B*, record taken at anterior axillary line. Three heart sounds. The first element of the triple rhythm coincides with the A wave of the jugular phlebogram. No true first heart sound can be seen in *A*. Short late systolic murmur merges with the vibrations of the second sound, which is split. There is an added sound in early diastole. The mid-diastolic murmur was not recorded.

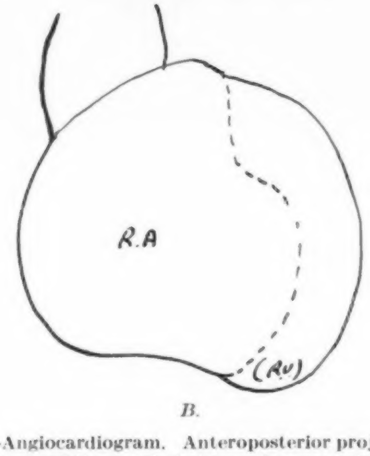
7. *Phonocardiogram.* A tracing taken from the cardiac apex demonstrated an early systolic murmur and additional sounds in early and late diastole.

Diagnosis.—Ebstein's anomaly of the tricuspid valve to a mild degree was present. Interatrial communication with a right-to-left shunt.

Comment.—Although the diagnosis has not been finally substantiated in this case, the clinical criteria warrant a presumptive diagnosis of Ebstein's disorder.

Before discussing the diagnostic criteria for Ebstein's syndrome, mention must be made of a case of pulmonary stenosis with normal aortic root and right-to-left interatrial shunt in which certain angiocardiographic appearances suggested Ebstein's anomaly and illustrated the difficulties of differentiating between the two disorders.

A.



B.

Fig. 4, *A* and *B* (Case 1).—Angiocardiogram. Anteroposterior projection. (Film at three seconds.) The contrast medium fills the whole of the heart shadow a few seconds after the injection, and remains there up to seventeen seconds. No pulmonary artery filling detected. This suggests an enormous right auricle.

CASE 3.—The patient was a 7-year-old girl. Since birth, she had a heart murmur, dyspnea, and cyanosis. Her exercise tolerance was one-half mile on flat ground, a few stairs if taken very slowly, and there was no squatting.

Examination revealed a normally developed, intelligent girl with slight cyanosis; clubbing of fingers and toes; heart enlarged to the right and left of the sternum; systolic thrill, maximal in third and fourth left intercostal space; systolic pulsation in the second and third left intercostal spaces; harsh full systolic murmur, maximal third and fourth left intercostal spaces; pulmonary

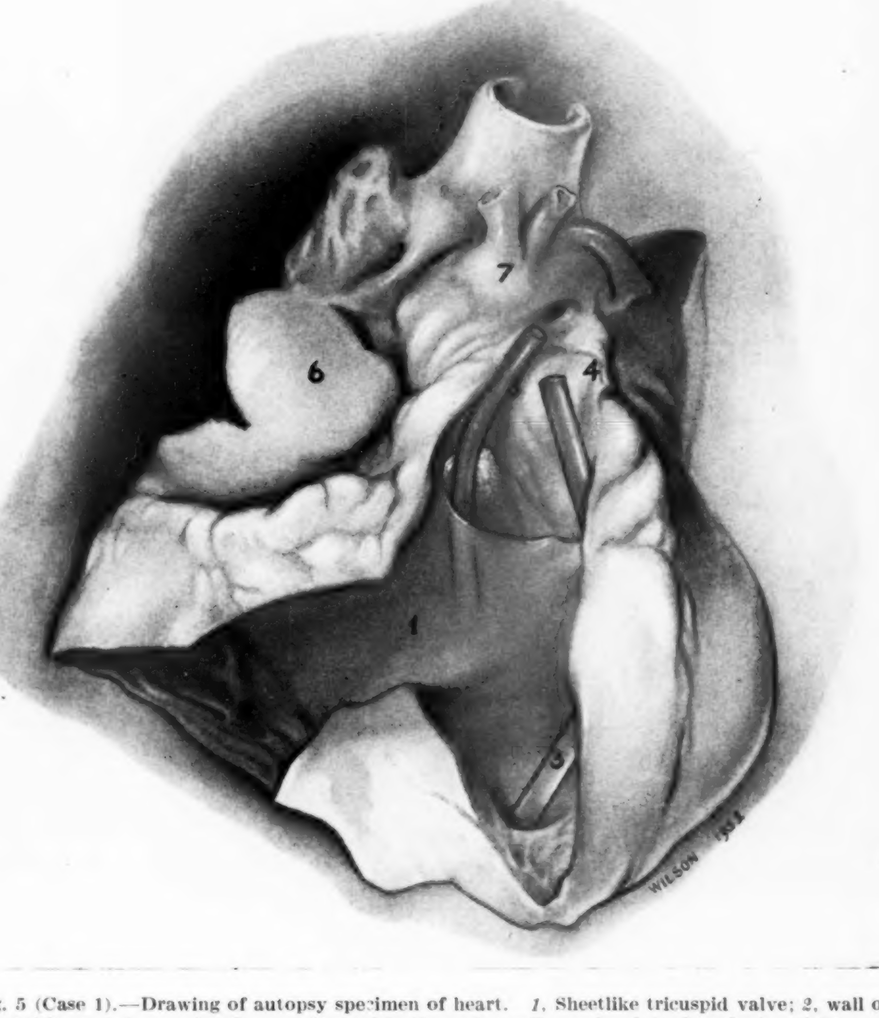


Fig. 5 (Case 1).—Drawing of autopsy specimen of heart. *1*, Sheetlike tricuspid valve; *2*, wall of right ventricle; *3*, tube passing from right auricle through small opening into functioning right ventricle; *4*, normal pulmonary valve and main trunk; *5*, tube passing through additional opening between right auricle and outflow tract of right ventricle; *6*, right auricular appendix, and *7*, aorta.

second sound split; early short diastolic murmur at apex; added sounds in mid-diastole and presystole; large cervical venous A wave; blood pressure of 90/60 mm. Hg; a small pulse. The liver was not enlarged nor pulsating.

Investigation disclosed the following:

1. *Blood*. Hemoglobin was 15 Gm. per cent, and arterial oxygen saturation 82 per cent.

2. *Fluroscopy* (Fig. 9) showed a globular-shaped heart which was grossly enlarged. There was an enormous right auricle and pulsation over the right ventricle. The left pulmonary artery was prominent, and the lungs were underfilled.

3. *Electrocardiogram* (Fig. 10) showed incomplete right bundle branch block, P pulmonale, right ventricular hypertrophy, and right auricular hypertrophy.

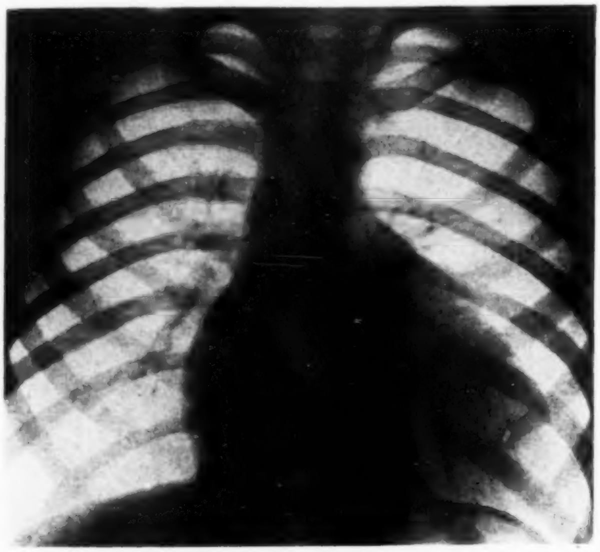


Fig. 6 (Case 2).—Plain roentgenogram of chest. Globular heart; large right auricle; (?) large right ventricle; pulmonary arteries not enlarged, and lungs underfilled.

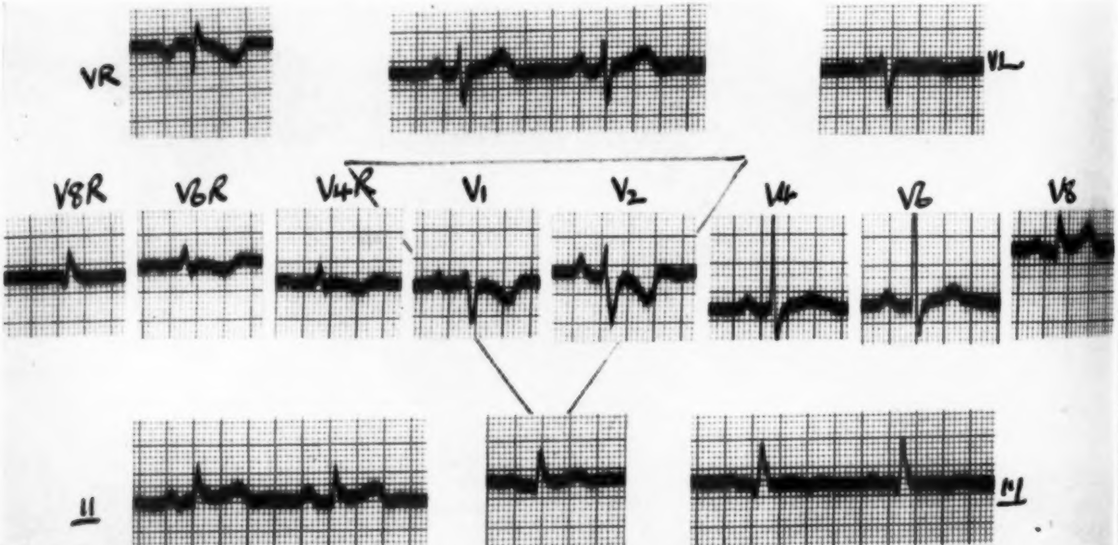
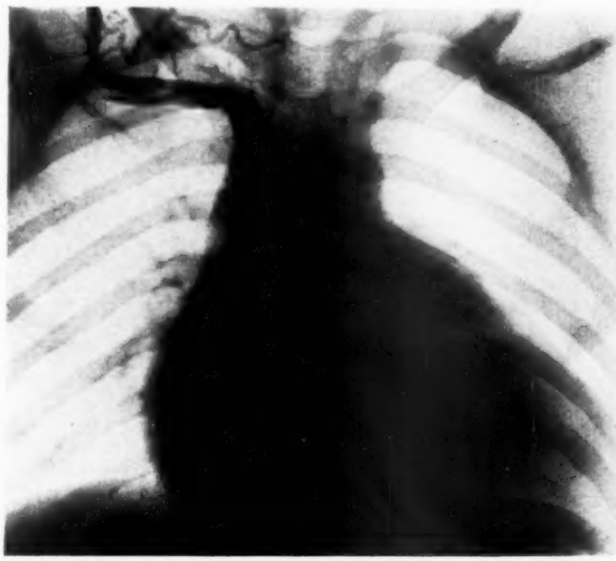


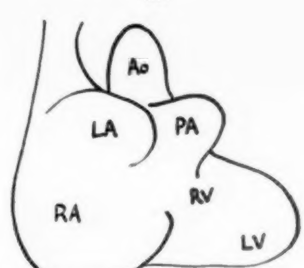
Fig. 7 (Case 2).—Electrocardiogram. Incomplete right bundle branch block. There is a rudimentary secondary R wave in V_{4R} suggesting incomplete right bundle branch block, but the ventricular activation time does not exceed 0.04 per second in this lead.

4. *Phonocardiogram* of the apex (Fig. 11). Three sounds were heard here: the auricular sound, a full systolic murmur, and a third heart sound. The jugular phlebogram showed large A wave, followed by a damped wave during ventricular systole, which was probably an artefact due to carotid arterial pulsation.

5. *Angiocardiogram* (Fig. 12, *A* and *B*). There was an enormous right auricle with displaced appendix and gross delay in emptying. The tricuspid notch was displaced to the left and opacification of the pulmonary arteries was delayed. Pulmonary stenosis could be seen, and probably



A.



B.

Fig. 8, *A* and *B* (Case 2).—Angiocardiogram. Anteroposterior projection. (Film at three seconds.) Large right auricle; contrast medium passes from right auricle to left auricle; later films show delay in emptying of right auricle; pulmonary arteries and lungs not well filled; tricuspid notch displaced to the left; aorta fills from left ventricle.

included valvular and subvalvular regions. The pulmonary vessels were not well opacified and no filling of the aorta was seen.

6. *Cardiac catheterization* showed the following: right ventricular pressure 125/0 mm. Hg, pulmonary artery pressure 8/5 mm. Hg, and no left-to-right shunt. (Dr. Paul Wood.)

Diagnosis.—Pulmonary stenosis with normal aortic root and right-to-left interatrial shunt; (?) anomaly of the tricuspid valve of Ebstein type.

Comment.—The added heart sounds, diastolic murmur, incomplete right bundle branch block, and angiocardiographic appearances of the right auricle gave rise to a suspicion of Ebstein's anomaly, but the pulsation over the right ventricular outflow tract and electrocardiographic signs of right ventricular hypertrophy were incompatible with this diagnosis. The presystolic added sound could

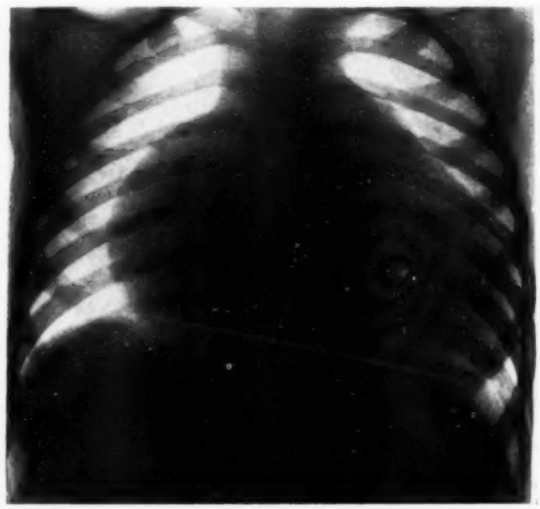


Fig. 9 (Case 3).—Plain roentgenogram of chest reveals: globular heart; very large right auricle and (?) right ventricle; left pulmonary artery prominent, and lungs underfilled.

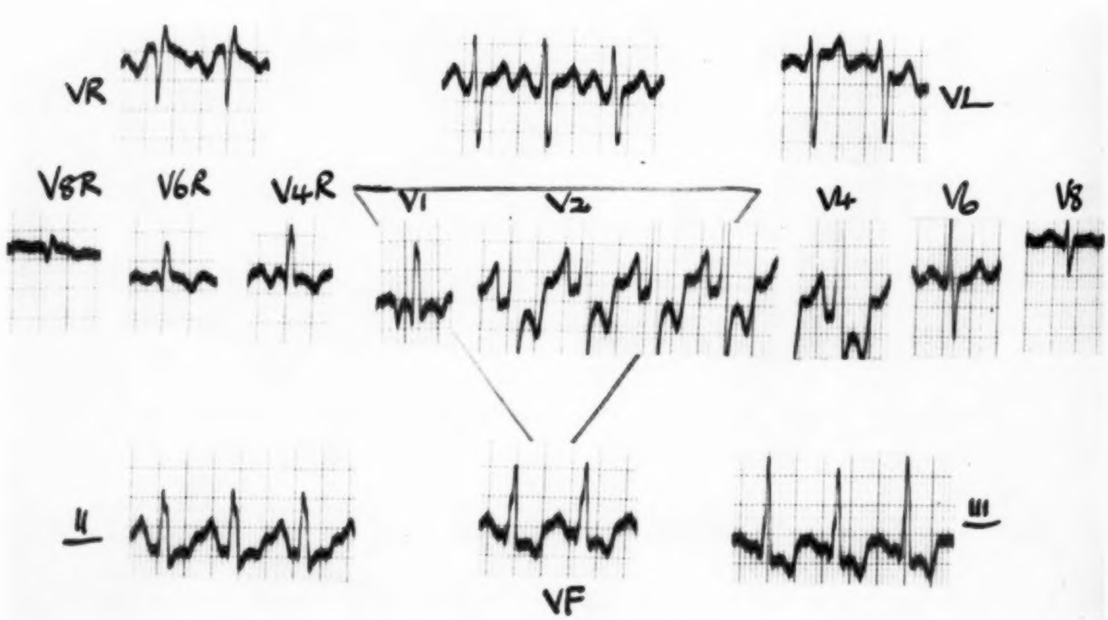
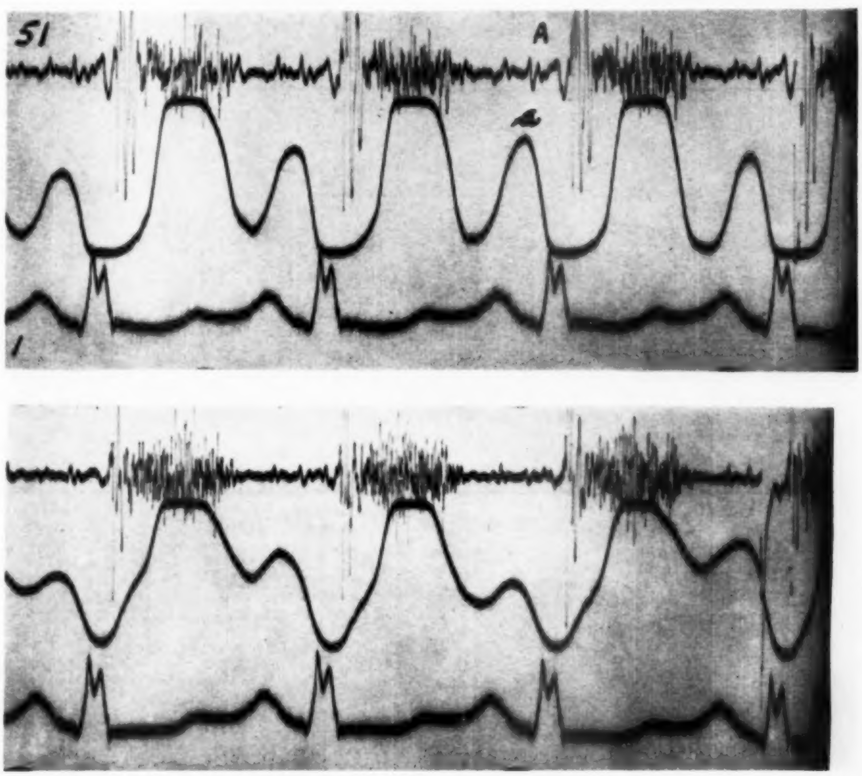


Fig. 10 (Case 3).—Electrocardiogram. Right ventricular hypertrophy; incomplete right bundle branch block; right ventricular hypertrophy marked and right auricular hypertrophy (P pulmonale).

be explained by the hypertrophied right auricle, the diastolic murmur by pulmonary incompetence, and the early diastolic sound by right ventricular failure. The angiocardiographic appearance of an enormous right auricle, displacement of the tricuspid notch to the left, and delay in emptying of the right auricle have not occurred in our experience in pure pulmonary stenosis. Moreover, they were similar to those seen in Cases 1 and 2. The great enlargement of the right auricle might be explained by hypertrophy and dilatation secondary to the right ventricular hypertension, and the prominent cervical A wave supported this contention. The delay in emptying might be explained by tricuspid incompetence, but there was no evidence of this clinically or on catheterization. It would



Apex
2: 2/8

Apex
4: 3/8

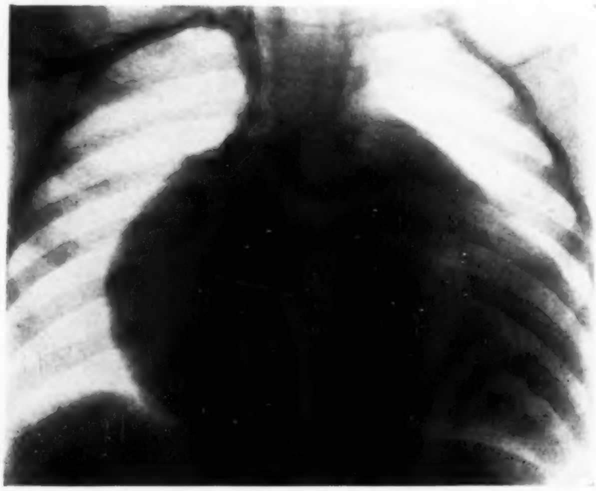
Fig. 11 (Case 3).—Phonocardiogram taken at the cardiac apex; jugular phlebogram, and electrocardiogram. Full systolic murmur; auricular sound; and third heart sound. Jugular phlebogram shows large A wave followed by a damped wave, probably the result of an artefact from the carotid artery.

appear that an anomaly of the right auricle may occur in pure pulmonary stenosis, and that this anomaly may present fluoroscopic and angiocardiographic appearances similar to those found in Ebstein's syndrome.

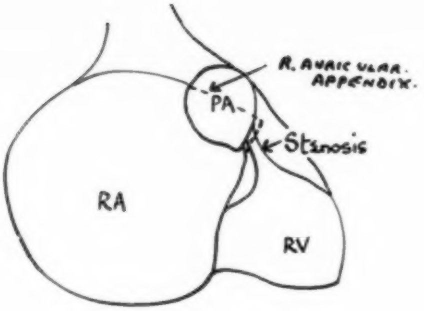
DISCUSSION

The malformation in Ebstein's syndrome[2] consists of fusion of the leaflets of the tricuspid valve into a membrane which extends downwards into the right ventricle like a sheet or basket and divides the right ventricle into two portions,

a proximal auricular portion and a distal ventricular portion. The valve leaflets may be completely fused with the endocardium of the ventricles so that the valve ceases to exist as such, and the orifice between the two portions of the right ventricle lies either between the free margin of the valve and ventricular septum or consists of an opening in the valve leaflet itself.[3] The foramen ovale is often anatomically and functionally patent, or there may be an atrioseptal defect.



A.



B.

Fig. 12 *A* and *B* (Case 3).—Angiocardiogram. Anteroposterior projection. (Film at five seconds.) The tricuspid notch is displaced to the left. There is delay in emptying of the right auricle, with displacement of the appendix. The pulmonary arteries are underfilled, and the stenosis can be seen. There is no aortic filling.

The malformation results in great dilatation of the right auricle, impairment of the action of the right ventricle, and therefore, of pulmonary artery blood flow and underfilling of the lungs. The increased right auricular pressure may be a factor in preventing closure of the foramen ovale, and a right-to-left auricular shunt with resultant central cyanosis may occur. An additional opening between the right auricle and pulmonary artery was found in our Case 1.

Up to date, thirty-two cases have been recorded, of which four have been diagnosed in life, but have not been confirmed at autopsy (Reynolds[7]; Soloff and associates[5]; Van Lingen and associates[4]). Case 1 presented in the present paper appears to be the only case in the literature in which an antemortem diagnosis has been thus substantiated.

Differential Diagnosis.—The three conditions with which this form of congenital heart disease is most likely to be confused are pulmonary stenosis with normal aortic root and with interatrial communication with right-to-left shunt; tricuspid atresia; and, the tetralogy of Fallot. In the severe cases, confusion with the tetralogy is unlikely, in view of the considerable cardiac enlargement in Ebstein's syndrome. The differential diagnosis has been discussed by Engle and associates.[3]

Clinical History.—This is unlikely to be of value, since the symptoms of dyspnea and cyanosis present from birth or delayed in onset may be common to all four conditions.

Clinical Signs.—The important differential clinical signs in Ebstein's disease, the tetralogy of Fallot, pulmonary stenosis with interatrial defect, and tricuspid atresia are set out in Table I. Cases may occur in which an exact differential diagnosis between tricuspid atresia and mild degrees of Ebstein's syndrome may be difficult, as in Case 2.

TABLE I. CLINICAL DIFFERENTIAL DIAGNOSIS OF EBSTEIN'S SYNDROME

CONDITION	FALLOT	EBSTEIN	TRICUSPID ATRESIA	PULMONARY STENOSIS WITH INTERATRIAL DEFECT
Cardiac enlargement	Slight to moderate	Moderate to gross	Slight to moderate	Moderate to gross
Cardiac pulsation	"Tapping" apex. Right ventricular type	Gentle, diffuse apex beat	Left ventricular type	Right ventricular type with sternal lift
Prominent A wave	±	+	+	++
Diastolic murmur	Usual	Unusual	Occasional	Rare
Triple rhythm	Rare	Common	Occasional	Usual

Radiologic Signs.—In the extreme form of Ebstein's syndrome, the cardiac silhouette may be almost diagnostic, if a pericardial effusion is excluded. The very large globular cardiac shadow, with great enlargement of the right auricle, feeble pulsation over the right ventricle, poorly visualized pulmonary arteries, and underfilled lung fields have been described by previous writers (Engle and associates[3]; Baker and associates[1]; Van Lingen and associates[4]). In tricuspid atresia the heart is often not markedly enlarged, and may be remarkably normal in appearance. Gross enlargement of the right auricle may occur in pulmonary stenosis, as in Case 3, so that the heart shadow may closely resemble that in

Ebstein's syndrome. The important differential points, as exemplified by Cases 1 and 3, are the pulsation of the right ventricle and dilation of the pulmonary artery in pulmonary stenosis, as compared with the quiet heart and normal pulmonary artery in Ebstein's disease.

Electrocardiographic Signs.—In Ebstein's syndrome, right bundle branch block is usual (Case 1), although this may be incomplete in type (Case 2). In the review by Baker and associates,[1] three out of four of the previously recorded cases in which an electrocardiogram was performed had right bundle branch block, as did the three cases described by Engle and associates,[3] the single case described by Soloff and associates[5] and the two cases mentioned by Van Lingen and associates.[4] In pulmonary stenosis, signs of right ventricular hypertrophy are present (Case 3), unless the condition is very mild. In tricuspid atresia, there is left axis deviation, sometimes with signs of left ventricular hypertrophy, but there is no evidence of right ventricular hypertrophy.

Auscultatory Signs and Phonocardiographic Findings.—Baker and associates,[1] reviewing the twenty-one cases published previous to their report, found mention of a diastolic murmur in only seven and concluded that this murmur was of no value in diagnosis. Engle and associates[3] found a diastolic murmur in only one out of their three cases, although it was present in both Van Lingen and associates' cases.[4] In view of the comparative rarity of a precordial diastolic murmur in other cyanotic congenital heart lesions with underfilled lungs, and its presence in the two cases reported here, this finding assumed greater importance. The added sounds are of even greater interest. A triple rhythm is commonly reported, and was present in our two cases. Phonocardiography, however, revealed four heart sounds in both cases, the presystolic sound presumably being due to the contraction of the dilated right auricle, in which the pressure was increased. Of particular note, in Case 1, was the apparent absence of the first heart sound to the left of the sternum, which might be due to the failure of closure of a normal tricuspid valve. The early diastolic sound might be due to the vibrations of the atonic ventricular muscle and the mid-diastolic murmur to the passage of blood through the communication between right auricle and ventricle. The presence of a normal pulmonary valve at autopsy makes it unlikely that the diastolic murmurs were due, as suggested by Baker and associates[1] in one of their cases, to pulmonary incompetence.

Angiocardiographic Signs.—The cardinal feature was a very large right auricle, with considerable delay in emptying. In Case 1, the right auricle occupied the whole of the heart shadow in the anteroposterior view. Because of the delay in the passage of dye into the right ventricle, the pulmonary arteries were poorly visualized and the lungs underfilled. In Case 2, the atrioseptal communication was large and the left auricle was seen to fill from the right auricle. In one of Engle's three cases, in Baker and associates' two cases and in Soloff and associates' case, the atrioseptal communication was clearly seen on angiocardiography. In our less severe Case 2, the tricuspid notch was seen displaced to the left. This presumably represented the portion of the abnormal valve sheet or basket which divides the ventricle into two portions. Soloff and associates[5] reported visualization of this structure, which showed as a small linear filling defect in the right

auricle. The angiocardiogram, in Case 2, was somewhat similar to that seen in tricuspid atresia, with the important difference that the right auricle was considerably enlarged (with displacement of the tricuspid notch); the triangular clear area in the position of the right ventricle was absent, and there was delay in emptying of the right auricle.

The main differences between the appearances in Ebstein's syndrome and pure pulmonary stenosis would appear to be that in the former condition the delay in the passage of contrast medium occurs in the right auricle, whereas in the latter it usually occurs in the right ventricle. In pulmonary stenosis the right auricle is seldom so large as in Ebstein's syndrome and the tricuspid notch is not displaced. However, it is clear from Case 3 that a very similar appearance to that in Ebstein's disease may occur in severe pulmonary stenosis, and that visualization of the stenosis may be essential in order to make the differential diagnosis by angiocardiographic means. Comparison of the angiocardiograms of Cases 1, 2, and 3 reveals the similarity.

Cardiac Catheterization.—As might be expected, failure to introduce the catheter into the right ventricle and pulmonary artery is common, the instrument coiling in the large right auricle (Baker and associates;[1] Engle and associates[3]). This occurred in the two cases reported here, although Van Lingen and associates[4] were successful in two patients thought to have Ebstein's disease. According to these workers, the characteristic findings are identical pressures in the right auricle and proximal portion of the right ventricle, without evidence of tricuspid insufficiency, a higher pressure in the distal portion of the right ventricle, but no fall in pressure on entering the pulmonary artery. Engle and associates[3] point out that the catheter may become entangled in the basketlike leaflets of the tricuspid valve, and that the procedure is fraught with more than the usual risk. Moreover, the known liability of these patients to paroxysmal arrhythmias is an additional hazard. In view of these risks and of the difficulty of entering the pulmonary artery, catheterization is unlikely to be of great value, but will continue to be employed in the investigation of such complex cases.

Degrees of Severity in the Ebstein Syndrome.—There is little doubt that wide variations in the severity of the condition occur (Engle and associates[3]). Most of the published reports deal with marked grades of tricuspid valve deformity—and little has been written about the diagnosis of the lesser degrees. The review of the published cases by Baker and associates[1] indicates that the condition may be compatible with considerable longevity. It is reasonable to suppose that the severity of the condition will depend upon the degree to which the abnormal valve is displaced into the right ventricle, and, consequently upon this, the size of the distal functional portion of this chamber, and the condition of its musculature. Slight degrees of displacement may result in only a moderately enlarged right auricle, adequate right ventricular function and pulmonary blood flow, and a good prognosis.

Surgical Treatment of Ebstein's Syndrome.—There has been no report of successful surgical treatment in a proven case of Ebstein's syndrome. With the exception of two cases (Taussig and associates[6]), the published cases which have been subjected to thoracotomy have been operated upon with the object of per-

forming an anastomotic operation or pulmonary valvulotomy in the mistaken belief that the condition was pure pulmonary stenosis or Fallot's tetralogy, and all have died. In our Case 1, it was felt that a subclavian pulmonary artery anastomosis was a reasonable procedure, and that the musculature of the right ventricle would tolerate the altered hemodynamic situation. Our assumption that the interatrial communication was large enough to act as an adequate safety valve was clearly incorrect, since at autopsy only a small patent foramen ovale was seen. It would appear, however, that the atrophic state of the ventricular muscle is unlikely to tolerate any operative interference that does not directly relieve the causal deformity.

An operative fatality in a severe case may not be anticipating the natural outcome by more than a few months or years, but if a fatal outcome follows thoracotomy in a milder case, then the patient's life may be cut short by a considerable number of years. Conversely, a patient with pure pulmonary stenosis in need of valvulotomy should not be denied operation because of an erroneous diagnosis of Ebstein's syndrome (Case 3).

An accurate diagnosis, therefore, is of great importance, and we believe that this can be made in the majority of cases if the combination of all the diagnostic findings is fully appreciated.

SUMMARY

A case of Ebstein's syndrome diagnosed in life and confirmed at autopsy is described with special reference to the clinical picture, angiocardiography, and phonocardiography. A second case, considered to be a milder form of the condition, is described, and the clinical features and results of special investigations are compared with those in the proved case. A case of severe pulmonary stenosis, in which the angiocardiogram, in addition to demonstrating the stenosis, presented features resembling Ebstein's syndrome, is also presented in order to emphasize the importance of differential diagnosis between the two conditions.

It is suggested that less severe degrees of displacement of the tricuspid valve may resemble tricuspid atresia, and the differential diagnosis from this and other conditions is discussed. It is concluded that surgery is unlikely to be of benefit in cases of Ebstein's syndrome, and that the diagnosis can usually be made by careful consideration of the clinical and fluoroscopic findings, assisted by angiocardiography and phonocardiography.

We wish to thank Professor E. J. Wayne for kindly referring Case 1, and Dr. R. E. Bonham-Carter for Case 3. Dr. Paul Wood kindly gave valuable advice on Cases 1, 3, and we are indebted to him for his catheterization findings. Our thanks are also due to Mr. E. V. Wilmot and his staff for the photographs and to Miss Wilson for the drawing of the heart in Case 1.

REFERENCES

1. Baker, C., Brinton, W. D., and Channell, G. D.: Guy's Hosp. Rep. **99**:247, 1950.
2. Ebstein, W.: Arch. f. Anat. u. Physiol. p. 238, 1866.
3. Engle, M. A., Payne, T. P. B., Bruins, C., and Taussig, H. B.: Circulation **1**:1246, 1950.
4. Van Lingen, B., McGregor, M., Kaye, J., Heyer, M. J., Jacobs, H. D., Braudo, J. L., Bothwell, T. H., and Elliott, G. A.: Am. Heart J. **43**:77, 1952.
5. Soloff, L. A., Stauffer, H. M., and Zatuchni, J.: Am. J. M. Sc. **222**:554, 1951.
6. Taussig, H. B., Padmavateyra, S., and King, J. T.: Proc. du 1° Congrès Mondial de Cardiologie, III, No. 312, p. 241, 1952.
7. Reynolds, G.: Guys. Hosp. Rep. **99**:226, 1950.

Book Review

THE AURICULAR ARRHYTHMIAS. By Corday, E., Brill, I. C., Oblath, R. W., Kruger, H. E., and associate authors. Springfield, Ill., 1952, Charles C Thomas, Publisher, 387 pages, 323 figures.

In this monograph, the authors have presented the results of their experimental work on the auricular arrhythmias together with a survey of both experimental and clinical literature on this subject. An excellent correlation has been made between the arrhythmias produced in the experimental animal (dog) and as they occur in man. The greater part of the book is the presentation of experimental data in support of their contention that the auricular arrhythmias (premature beats, paroxysmal tachycardia, flutter, and fibrillation) differ in degree rather than in the nature of the underlying condition. A large part of the work presented consists in a re-evaluation and refutation of the circus movement theory of Sir Thomas Lewis as the underlying mechanism of auricular flutter and fibrillation. They observe at the start of this discussion that Lewis had presented a theory which he did not consider to be fully supported, but that this theory has generally been accepted as fully documented by experimental data.

New methods have been used in the attack upon this old problem. Dramatic moving pictures of auricular movement have been made by high-speed cinematography permitting exposures up to 3,000 frames per second. When they are projected at a rate of 8 frames per second, events, which were completed in one second, required six minutes of projection. By this means it was possible to visualize normal and abnormal auricular movement in the experimental animal and in the human auricle at operation. It was apparent to these investigators that the auricular movement in extrasystoles, paroxysmal tachycardia, and flutter was identical. In each instance the wave of contraction arose from a single focus, and by whatever means the arrhythmia was produced, the form of the contraction wave was the same. If electrical stimulation was employed, the particular arrhythmia which resulted depended upon the rate of stimuli. For example, auricular fibrillation occurred only at the most rapid rates of stimulation, 400 to 600 per second, and if aconitine was applied, only at the higher concentrations of this solution. It was thus observed, that regardless of the method of production, the rate of discharge of stimuli from the focus determined which arrhythmia occurred. In auricular fibrillation, however, the motion of the auricles differed greatly from the other arrhythmias, and two component movements were demonstrated. A larger, more diffuse contraction was known as the "L" type and a smaller, more rapid one was labeled the "M" type. The fibrillary waves of the standard electrocardiogram were related to the "L" contractions.

Although no circus movement was demonstrated in flutter or fibrillation by these cinematographic techniques, the problem was also investigated with the use of the multiple channel electrocardiograph and the dual beam cathode-ray oscillograph. Esophogeal lead studies were made. Particular study was directed toward the electrical events occurring in the left auricle where the "gap" lay in Lewis' experiments. The authors were unable to report any observations favoring a circus type of movement.

The format, photographs, electrocardiograms, and diagrams of the monograph are excellent. There are interesting and useful discussions on the pharmacologic action of antiarrhythmic drugs and on the treatment of the auricular arrhythmias occurring clinically. The monograph is an outstanding contribution to the study of the auricular arrhythmias and a well-conceived presentation and correlation of experimental, clinical, and therapeutic aspects of this subject.

A.J.

CARDIAC THERAPY. By Stewart, Harold J. New York, 1952, Paul B. Hoeber, Inc., 622 pages.

This is the first comprehensive presentation of cardiac therapy in book form that has appeared in recent years. It is so well done that it will serve as a model for others. The great

strength of this book lies in the fact that it has been written entirely by Dr. Stewart who has had years of experience at New York Hospital treating patients with heart disease. Throughout the book not only are all the modern forms of therapy adequately discussed, but the practical application to the patient is constantly stressed because Dr. Stewart has personally evaluated these forms of therapy and expresses his opinion of their worth.

The discussion of therapy is conservative and intensely practical with a great deal of detail. The book is primarily written for the student and general practitioner rather than for the cardiac specialist who may find the text too elementary for his liking. However, the book is entirely up to date and includes an evaluation of all new drugs advocated for cardiac conditions as well as other forms of therapy such as surgery.

The treatment of congestive heart failure is placed first in the book. To the reviewer, this seems to be the best spot because heart failure occurs in many types of heart diseases.

Diagnosis could not be entirely left out because good treatment will in many cases depend on accuracy of diagnosis. Dr. Stewart, therefore, included some material on diagnosis in the beginning of each chapter, but has wisely kept a discussion of diagnosis to a minimum.

A.C.D.

CLINICAL PROGRESS IN CARDIOVASCULAR DISEASE. By Blumgart, Hermann L. New York, 1952, Grune & Stratton, Inc.

This small volume consists of five reviews which have been selected from those appearing under the section "Clinical Progress" in *Circulation*. They have been chosen as dealing with subjects in which much work is being done at the present moment and which have in addition a practical application. Almost one-half the book consists of a discussion of the current views on the etiology of arteriosclerosis, a topic of vast interest at present. In addition there are discussions on acute cardiac emergencies, surgery in mitral stenosis, the management of cardiac patients in relation to surgery, emotions, and the circulation. The articles are all excellent and bring the subjects fully up to date at the time that they were published. The subjects are clearly and simply presented so that extremely specialized knowledge is not required in order to comprehend them. Presumably, the object in publishing the book is to disseminate the knowledge contained beyond the field in the medical profession which usually reads *Circulation*. Any physician will obtain a great deal of valuable information from these critical views.

J.H.C.

ANNOUNCEMENT

The University of Minnesota will present a continuation course in "Recent Advances in Diagnosis for internists" at the Center for Continuation Study on Feb. 16 to 18, 1953. Although intended primarily for specialists in internal medicine, the program will be of interest to many pediatricians and general physicians. This course will provide information concerning techniques which have been introduced or developed within the past five to ten years, which have increased our knowledge of basic physiology, and which are becoming or give promise of becoming standard diagnostic procedures. Recent developments in the fields of cardiology, respiratory disease, renal disease, hematology, gastroenterology, and endocrinology will be emphasized.

Under the direction of Dr. C. J. Watson, Professor and Director of the Department of Medicine, an outstanding guest faculty has been assembled: Dr. Carl V. Moore, Professor, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; Dr. Thomas E. Machella, Assistant Professor, Department of Medicine, and Associate in Physiology, University of Pennsylvania School of Medicine, and Chief of Gastrointestinal Clinic, Hospital of the University of Pennsylvania, Philadelphia; Dr. Robert P. Grant, U. S. Public Health Service Hospital, Baltimore; and Dr. William W. Engstrom, Associate Professor, Department of Medicine, Marquette University School of Medicine, and Director, Metabolism Section, Milwaukee County Hospital. The remainder of the faculty will include clinical and full-time members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

Lodging and meal accommodations are available at the Center for Continuation Study.